CLINICAL FEATURES AND MANAGEMENT OF LASSA FEVER.

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OUTLINE

- Introduction
- Transmission
- Clinical course
- Mortality issues.
- Pregnancy issues
- Diagnosis
- Investigations
- Management
- Conclusions .

INTRODUCTION

- Viral haemorrhagic fever (Arena virus)
- First discovered in Nigeria in 1969
- Now seen in almost all west African countries
- Most common exported VHF
- Causes significant morbidity and mortality
- Now endemic in some communities in Nigeria
  - With seasonal peaks in the dry season.
  - In 2022, 941 confirmed cases,173 deaths CFR 18.4% (Nigeria) NCDC.
- In 2018, WHO listed it as a priority disease needing countermeasures.

TRANSMISSION

- The Lassa virus is transmitted from rat to humans

- Ingestion of food contaminated with the urine, faeces or blood of infected mastomys.
- Handling, killing or ingesting infected rats.
- Inhalation of aerosolized virus through droplet transmission.
  - During cleaning of surfaces.
  - Sweeping of floors containing infected rat droppings.
  - But true airborne transmission is unlikely.

TRANSMISSION (CONTD)

- Human to human transmission
  - mainly in health care setting when there is
    - direct contact with blood, body fluid of infected patients
    - unsafe injection practices.
    - Contact with contaminated bed railings, bed linens and medical equipment
    - Skin cuts, abrasion or wounds facilitate transmission.

- Sequencing data shows that majority of transmissions are from rats to humans; and human to human transmission even in the same household is uncommon. This contrasts with Ebola where majority of transmission is human to human.

TRANSMISSION (CONTD)

- Recent evidence suggest that sexual transmission is possible
- Virus persistence in semen for up to 12 months after discharge.
- Infectivity of persisting virus was recently demonstrated by researchers from the ISTH and BNITM.
- Congenital transmission from mother to fetus or newborn.
- Transmission via breast milk, due to the high viral load in breast milk[54,55].

CLINICAL COURSE

- The infection is asymptomatic in 80% of people.
- In 20% of people symptoms vary from mild to severe.
- Death complicating about 1% of infected persons.
- However, during epidemics, mortality rate for hospitalized patients can be as high as 15-40%.
- The case fatality rate for hospitalized patients in Nigeria is currently about 20%.

CLINICAL COURSE (CONTD)

- In pregnant patients, Lassa fever presents special challenges in diagnosis, management and outcome.

- In non-pregnant women, mortality..13%, while in pregnancy….30%
- Perinatal mortality…. 85-95% during epidemics.
- high abortion and IUFD.

- In endemic communities, Lassa fever disease contributes as much as 13.1-25% to the overall maternal mortality figures[59].

- Addressing the challenges of pregnant women should be prioritized.

CLINICAL COURSE.

- The incubation period is.. 2 to 21 days.
- illness last for 3 weeks resulting in recovery or death.
- The disease has an insidious onset.
- initial symptoms are mild and varied.
- At this stage, it is often taken lightly
  - presumed to be malaria, typhoid fever or gastroenteritis.
- The advice in endemic communities… screen patients for Lassa, if no response to antimalarials or antibiotics after 48 hours of treatment.

INDEX OF SUSPICION

- History of non-response to antimalarias and antibiotics
- History of travel to endemic areas or areas with ongoing outbreak
- Contact with a confirmed case

CLINICAL FEATURES

- The initial symptoms are
  - **fever (temp >38^{oc}), malaise, headache, loss of appetite, weakness and body pains.**
- More specific symptoms appear a few days later
  - **pharyngitis, cough, retrosternal chest pain, abdominal pain, nausea, vomiting, diarrhoea.**
- Further symptoms are usually due to complications.
- Disseminated Intravascular Coagulation (DIC)
  - **petechial and conjunctival haemorrhage, ecchymosis, haematuria, haemoglobinuria, haemoptysis, haematemesis, nose bleeding.**
  - **However, despite the fact that Lassa fever is a viral haemorrhagic fever, less the 30% actually have haemorrhagic symptoms**[3,56,60,]

CLINICAL FEATURES (CONTD)

- Acute Kidney Injury
  - **oliguria, facial, pedal oedema and generalized oedema**.
- Acute respiratory distress syndrome
  - **dyspnoea and reduced SPO_2**.
- Encephalopathy or Central nervous system involvement.
  - **Delirium, seizure, tremors, hiccups and coma**.
- Hepatic involvement.
  - **Jaundice with tender hepatomegaly.**
- In many settings patients often present late when complications have already set in.
  - **Unilateral or bilateral deafness** of varying decree occurs in about one third of patients.
    - This could be **temporary or permanent**.

CLINICAL FEATURES (CONTD)

- Death usually results from
  - **Acute Kidney Injury.** (81/284 persons ie 28% had AKI and 60% 49/81 of them died). Intrinsic renal damage.
  - **Encephalopathy and seizures.** (37% had CNS manifestation)
  - **Acute respiratory distress symptoms.** 10/65 had pul involvement with 70% mortality. As against 38.2% without pulmonary involvement. Amother study in Abakaliki showed between 25 to 76.8% respiratory distress.
  - **Sepsis and shock**.
  - **Bleeding**
  - **Psychiatric and Psychological distress** (36.8% reported Psychological distress and 40.6 met criteria for Psychiatric disease)

- Spontaneous recovery can occur in cases that do not progress to organ damage.

LASCOPE STUDY

- NEWS (national early warning score of 7 or more (LASCOPE STUDY Alexandre D.
- KIDGO STAGE 2 AND ABOVE (67/495, 14% OF PATIENTS AND 8% NEEDED DIALYSIS

CLINICAL COURSE IN PREGNANCY

- It is not clear whether there are as many asymptomatic cases as there are in non-pregnant patients.
- In symptomatic patients, the disease starts insidiously after 2 to 21 days of incubation
- Symptoms are similar to those seen in non-pregnant individuals.
- There are however symptoms specific to pregnancy.
- In **first trimester**, patients could present with
  - Hyper-emesis associated with other Lassa fever symptoms.
  - Abortion is common in the first trimester and may be the only presenting complaint.
  - At presentation in the first trimester, the fetus is usually not viable.
  - Spontaneous abortive process may even be complete.
  - An ultrasound scan done at this stage will confirm the state of the uterus.

FIRST TRIMESTER CONT.

- In endemic communities, Lassa fever must be suspected in patient with unexplained fetal loss that has been associated with a preceding febrile illness.

- Early screening should be done for pregnant women with fever or ill health unresponsive to antimalaria and antibiotics.

SECOND / THIRD TRIMESTER

- In the late second or third trimester, there are two broad categories of presentation.

In the first category:

- Fetus is viable
- Symptoms are mild such as fever, malaise, headache and body pain.
- No signs of complication,
- Suggesting an early presentation or a mild disease.

The second broad category:

- Non-viable fetus.
- Signs of severe disease such as extra vaginal bleeding, coma, seizure, sepsis, oliguria etc[59].
- The disease is fulminant and can progress rapidly to maternal death.
- The presence of a dead fetus in the third trimester is therefore an emergency which requires urgent evacuation of the contents of the uterus preferably via the vagina route.
- The stress of surgery in this category of patients may result in poor outcome.

OTHER SPECIFIC FEATURE SEEN IN PREGNANCY

- The breast sign.
  - One or both breasts may become enlarged, turgid and painful
  - without secretion of milk or colostrum.
  - The cause of this breast sign is unknown
  - but it appears pathognomonic.
  - May be immune mediated
  - Good prognostic sign

OTHER SPECIFIC FEATURE SEEN IN PREGNANCY (CONTD)

- It is known that breast milk may contain the virus during puerperium
- The breast may be a sanctuary site for persistent virus even after clearance from the blood.
- Persistent virus in some body fluids several months after discharged following a negative serum PCR.

- Vaginal bleeding may also present in Lassa fever in pregnancy in the third or late trimester and can often be misdiagnosed as antepartum or postpartum haemorrhage from abruptio placenta or placenta previa.

PROGNOSIS IN PREGNANCY

- The worse prognosis seen in pregnancy has been attributed to various factors.
- The insidious, non-specific and varied nature of symptoms in the early stages of lassa fever disease mimic early/constitutional pregnancy symptom or the general lassitude of pregnancy.
- Causes delay in presentation and delay in making an accurate diagnosis with consequently poor outcome.
- The Lassa fever virus has a higher affinity for the vascular tissues of the fetus and placenta.
- The maternal immunity is significantly altered in pregnancy
- The fetal immunity is still maturing.
- The result is that pregnant women harbor significantly higher viral load than in the non-pregnant state
- High viral load has implication for overall outcome.

PROGNOSIS IN PREGNANCY CONT.

- In severe cases of lassa fever disease when complications set in,
- Pregnant women may present with
  - **Seizures,**
  - **Haemorrhage and**
  - **Sepsis.**
- These 3 presentations of lassa fever disease mimics
  - **Eclampsia,**
  - **Obstetric haemorrhagic**
  - **Pregnancy related sepsis;**

the three commonest Obstetric causes of Maternal mortality.

- Hence the diagnosis of Lassa fever can be easily missed and thus Lassa fever may be a **HIDDEN** cause of many maternal mortality in endemic areas of West African[59].
- In Irrua and Sierra Leone LF contributes 13 to 25% to maternal mortality fiqures. This is significant. Lassa fever is thus a **SIGNIFICANT** cause of maternal mortality in endemic communities.

- Maternal Mortality figure in Nigeria is high and it is recalcitrantto may interventions,

- Lassa fever may be a **HIDDEN** yet **SIGNIFICANT** contributor to the recalcitrant maternal mortality figures in Nigeria and other endemic countries.

- It is not uncommon to see Obstetricians/Doctors infected with lassa fever after a caesarean section for a pre-operative diagnosis of eclampsia or haemorrhage.

INVESTIGATION

- A confirmatory test is necessary to establish the diagnosis.
- This is often done with a real time RT-PCR.
- Lassa fever can also be diagnosed using enzyme-linked immunosorbent serologic assays that detect
  - IgM
  - IgG
  - Lassa antigen.
- Viral culture is usually for research purposes and
- Immune-histochemistry can be done on post-mortem tissues.

MANAGEMENT

- A confirmatory test is necessary to establish the diagnosis.
- Patients are then admitted into a Lassa fever isolation facility
- Manage under standard and additional IPC measure to prevent contact transmission.
- A multidisciplinary team approach is best to provide optimum care.
- An infectious disease physician and an obstetrician with interest in infectious disease are vital for the management of pregnant patients
- Other specialist that may be needed in the course of treatment include a
  - Nephrologist,
  - Haematologist
  - Critical care physician.

INVESTIGATIONS

- The base line investigations for all patients include
    - FBC, platelet count,
    - blood sugar,
    - clotting profile,
    - E/U/C estimation,
    - LFT with AST and ALT.
    - Urinalysis for proteinuria and microscopic haematuria.
- These investigations should be repeated on day 5 and day 10 for patients with mild disease who are responding to treatment.
- It is important to rule out other common causes of fever in the communities
- Blood test for malaria parasite and typhoid fever.
- Urine M/C/S to rule out urinary tract infection.
- These infections can co-exist with lassa virus disease.

- Severely ill patients OR worsening disease will need more frequent repeat investigations

- These could be done every 48hours.

- More investigations are also necessary for severely ill patients.

- These could include blood gasses, blood culture, serum calcium, chest X-ray or CT-Scan, EEG and ECG.

TREATMENT (CONTD)

- Treatment is often commenced immediately with intravenous ribavirin using the McCormick multiple daily doses or
- the Irrua regimen which is a single daily dose.

- Supportive care with intravenous fluid,
- Prophylactic antibiotics with intravenous ceftriaxone or Augmentin.

- Oxygen therapy and blood transfusion may also be required.

- When complications threaten or set in, the necessary specialist should be consulted early.
- Dialysis is often required for acute kidney injury.
- Aminoglycosides and other nephrotoxic drugs are best avoided.
- Intravenous crystalloids and vasopressors are needed in shock.
- Low dose haloperidol is useful to treat delirium and
- anticonvulsants may be given when there is seizure.
- Respiratory distress could require ventilatory support.

MANAGEMENT IN PREGNANCY

- An ultrasound scan to determine the state of the fetus and course of management to be adopted.
- This should be done on the day as soon as possible.
- The ribavirin regime used in the Irrua Specialist Teaching Hospital for Pregnant women is the Modified McCormick regime.

IN THE FIRST TRIMESTER:

In the first trimester,

- Abortion is the rule and many patients present with an ongoing abortive process.
- An ultrasound scan done to confirm an inevitable, incomplete or missed abortion.
- Commence on intravenous ribavirin, supportive care with intravenous infusion and prophylactic broad-spectrum antibiotics.
- An immediate evacuation of the contents of the uterus is done whenever there is a diagnosis of inevitable, incomplete or missed abortion.
- Ensure the uterus is completely empty, retained product could prolong the duration of the fever with poor prognosis.
- An USS 48 hours after the evacuation is recommended to ensure the uterus is empty if in doubt.

IN THE SECOND THIRD TRIMESTER:

• In the late **Second/Third trimester**, the two broad categories described earlier become relevant.

In the **first category** in which the symptoms are mild and importantly the fetus is viable:

- conservative management with intravenous ribavirin and supportive care give better outcome for the mother and the foetus.
- In such circumstances the patient is also given prophylactic antibiotics, analgesics and haematinics.
- Dexamethasone injection is often given for fetal lung maturity because of the high risk of preterm birth.
- However, tocolytics are to be avoided.

CONSERVATIVE MANAGEMENT FOR FIRST CATEGORY.

- Maternal and fetal monitoring is vital when on admission for conservative management.
- Fetal well-being is monitored with at least twice daily fetal heart rate check with a hand-held doppler.
- Baseline and weekly biophysical profile or a non-stress test
- This ensures fetal compromise or intrauterine fetal demise is immediately recognized.
- Maternal vital signs are monitored by temperature checks, blood pressure and pulse rate measurements.
- Real time PCR checks are also done on day 5 and day 10 of treatment to determine the CT values and estimate the viral load.
- In the vast majority of patients, symptoms gradually abate and at about day 10, many patients have a negative PCR and are then moved from the isolation ward to a regular ward.
- Those still positive are treated for a few more days with the daily ribavirin dose until the PCR is negative otherwise a decision for delivery could be taken at this point depending on the gestational age, fetal wellbeing and the severity of maternal symptoms or illness.

CONSERVATIVE MANAGEMENT FOR FIRST CATEGORY. (CONTD)

- When the PCR is negative and maternal symptoms have abated, patients are transferred to regular wards for continuous fetal monitoring until delivery.
- intrauterine fetal death could still occur in about 30-50% of surviving fetuses.
- Fetal monitoring is done with twice daily fetal heart rate monitoring with the hand-held doppler and also twice weekly biophysical profile or non-stress test.
- Delivery is initiated at 37 completed weeks or if fetal well-being test are non-reassuring.
- Vaginal delivery is to be preferred except there are obstetrics reason for a caesarean section.

SECOND CATEGORY IN SECOND/THIRD TRIMESTER

There is intrauterine fetal death.

- This is often associated with symptoms of severe disease or organ involvement.
- Patients could present with severe symptoms of DIC, AKI, ARDS, Seizure and coma are ominous signs.
- In this circumstance, the disease is often fulminant and can quickly progress to death.
- There is an urgent need to evacuate the dead fetus, placenta and membranes.
- This gives the best chance of survival.
- Unfortunately, evacuation may not be achieved and many such patients die undelivered.
- Evacuation and other necessary treatment should go on simultaneously with dialysis, blood and blood product transfusion, intravenous ribavirin, intravenous antibiotics, vasopressors, ventilation and other critical care measures.
- However, should a vaginal delivery occur Amazing recovery can be achieved. This is very well worth the effort.

• It is important to note that during conservative management of pregnant women with mild disease, intrauterine fetal death could occur. In such circumstances, evacuation should be conducted immediately, however the patients are usually not in fulminant disease and the delivery could be conducted safely with good maternal outcome.

CONDUCT OF DELIVERY

- In all circumstances, delivery is conducted with standard and additional precautions to avoid contact transmission.

- The cord blood is taken for PCR and when positive, the newborn is handed over to the pediatricians for specialist care.

- When negative, Neonates can be re-tested 2-3 weeks later or if illness ensues.

- Neonates born to mothers who have had some days of treatment often do better than neonates of mothers who are delivered before treatment could be initiated.

- At delivery, the breast milk should be tested for lassa virus by PCR and if negative, the newborn can be breastfed otherwise artificial milk is given until the breast milk has a negative PCR result.
-

- Multiple pregnancy is commonest in west Africa so is LF
- It is not unusual to see lassa fever infection complicating twin pregnancies.
- The presentation and management are essentially as in the singleton pregnancy.
- However, if during conservative management one twin dies, then delivery should be initiated and outcome is essentially as in singleton pregnancy.

	Clinical features	
Initial features	Fever, headache, malaise, body aches and pains	
More specific features	Sore-throat, retrosternal chest pain, cough, nausea, vomiting, conjunctival haemorrhage, proteinuria, microscopic haematuria.	
Features of complications	Acute kidney injury	Oliguria, pedal and facial oedema, confusion and seizure
	Acute respiratory distress syndrome	Dyspnoea, tachycardia, reduced SPO2.
	Disseminated intravascular coagulation	Petechial haemorrhage, ecchymosis, Haematuria, haemoptysis, vaginal bleeding, bleeding from the gum and oral mucosa.
	Encephalopathy	Delirium, restlessness, seizure, coma.
	shock	Low blood pressure, increased pulse rate.
	Liver involvement	Jaundice, elevated AST, elevated ALT, tender hepatomegaly.
Symptoms specific to Pregnancy.	Hyperemesis, Abortion, prematurity, intrauterine fetal death, vaginal bleeding. Breast sign: enlarged, turgid and tender.	

LASSA FEVER IN PREGNANCY. CATEGORY 1: FETUS IS VIABLE AND SYMPTOMS ARE MILD.

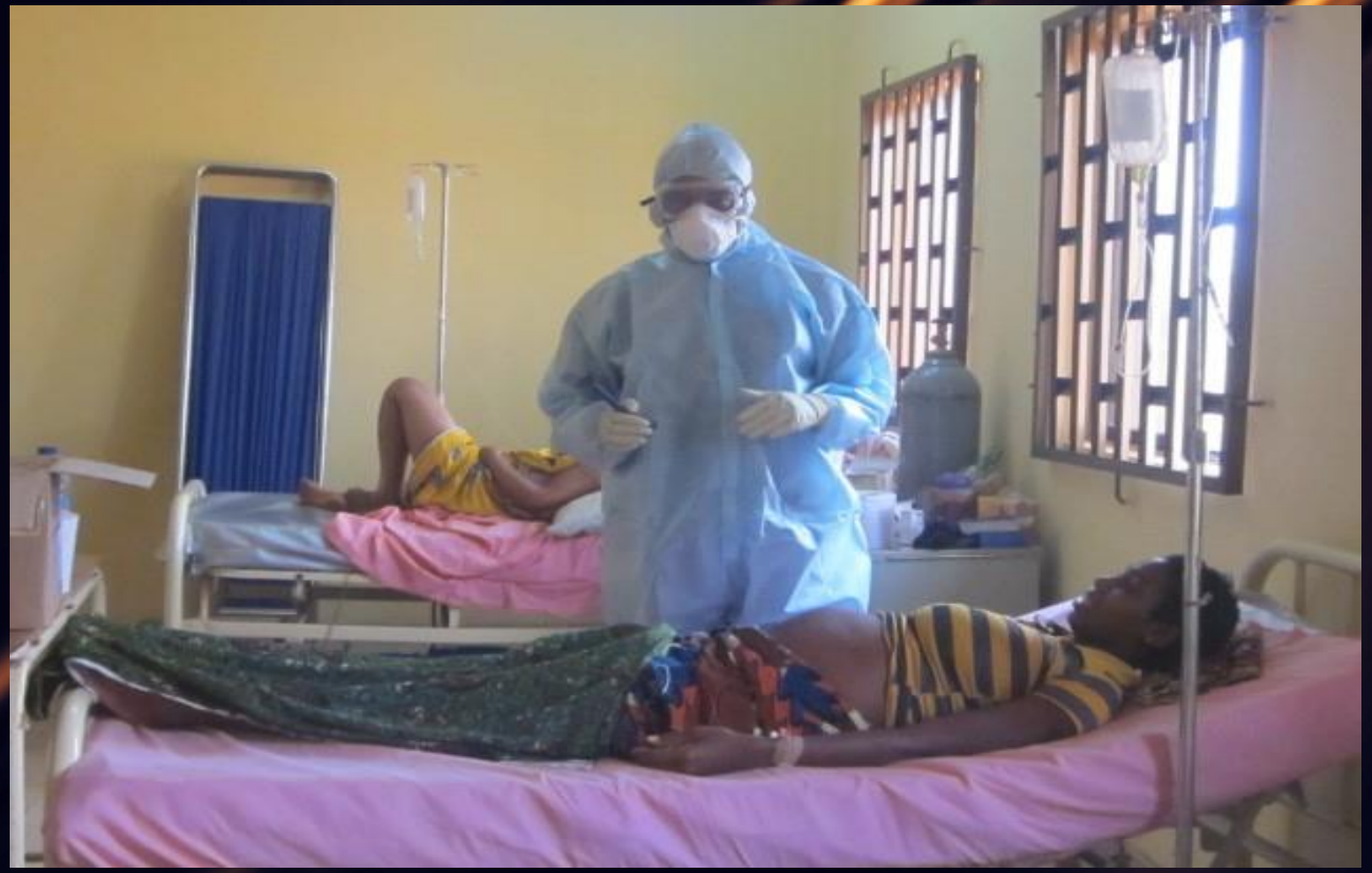
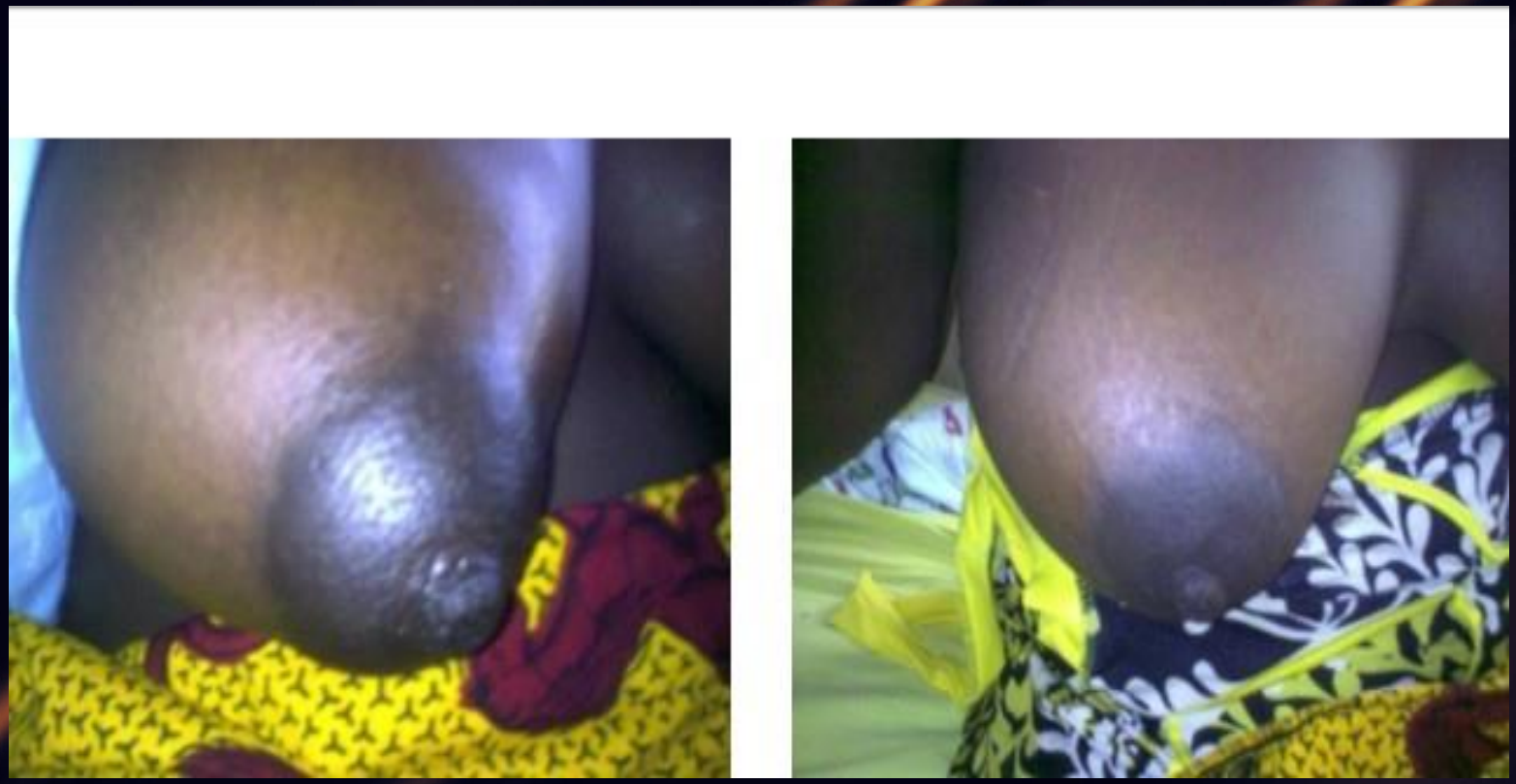


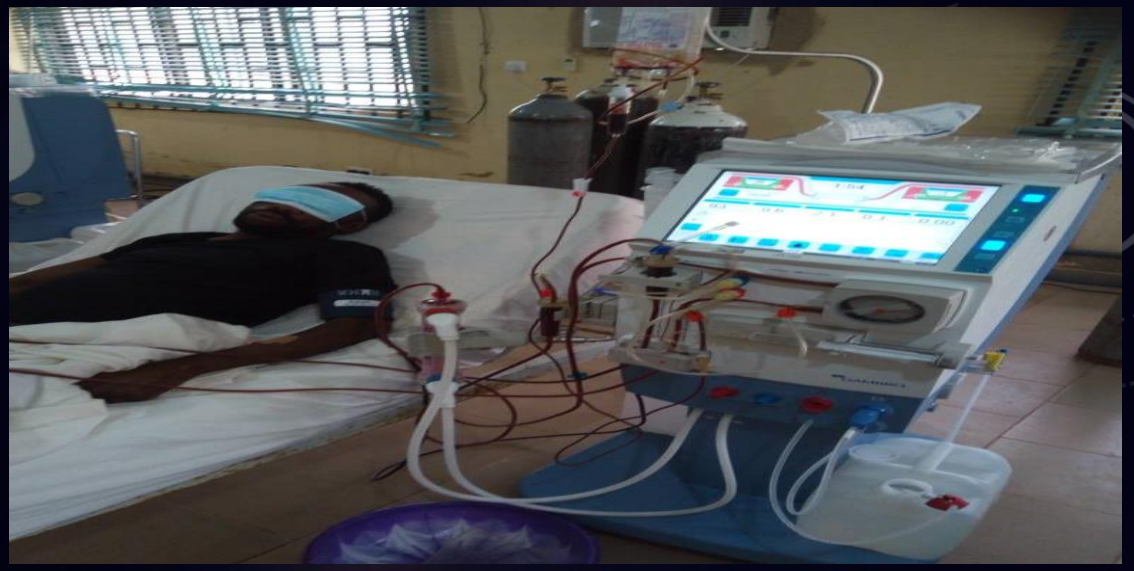
FIGURE 2, LASSA FEVER IN PREGNANCY. CATEGORY 2: FETUS IS DEAD, PATIENT HAS SEVERE SYMPTOMS. BLOOD IN URINE AS SEEN IN THE URINE BAG, FOOT OF BED IS RAISED BECAUSE PATIENT IS IN SHOCK. OXYGEN IS BEING DELIVERED WITH A NASAL PRONG.

FIGURE 3, BREAST SIGN IN LASSA FEVER IN PREGNANCY: BEFORE AND AFTER TREATMENT.



INTENSIVE AND CRITICAL CARE

DIALYSIS UNIT



INTENSIVE AND CRITICAL CARE

Thank you very much.