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Unexplained Recurrent Maternal Fever Leading To Fetal Demise: Role of Empirical Therapy For Successful Outcome

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ABSTRACT

Background: Pyrexia of unknown origin (PUO) during pregnancy is uncommon and poses significant diagnostic and management challenges. It may reflect underlying immune dysregulation, contributing to adverse fetal outcomes.

Case Presentation: We report a 26-year-old woman with recurrent mid-trimester high-grade fevers during two consecutive pregnancies, both ending in intrauterine fetal demise (IUFD). Extensive investigations failed to identify an infectious, malignant, or inflammatory cause. Placental histopathology revealed inflammatory changes. Lupus anticoagulant was later found to be positive. In her third pregnancy, early initiation of empirical immunosuppressive therapy—azathioprine, low-dose steroids, low-molecular-weight heparin, and aspirin—resulted in a successful outcome with delivery of a healthy infant.

Conclusion: PUO in pregnancy may be a manifestation of immune dysregulation or fetal allograft rejection. In select cases, empirical immunomodulatory therapy instituted preconceptionally or early in pregnancy may improve outcomes. A high index of suspicion and multidisciplinary management are crucial in such scenarios.

Keywords: Pyrexia of unknown origin, PUO, IUFD, Intrauterine fetal demise, Empirical treatment

INTRODUCTION

Fever in pregnancy is a common clinical problem with implications on the maternal and fetal health. Hyperthermia-induced fetal damage can be due to cell death, membrane disruption, vascular disruption or placental infarction [1]. There is a linear association between duration of fever and fetal outcomes which can rarely result in Intrauterine fetal demise. Most fevers during pregnancy are due to infectious causes such as Urinary Tract Infection, Respiratory tract infection, Malaria, Dengue or Hepatitis. Pyrexia of unknown origin (PUO) defined as clinically documented temperature >101°f or higher on several occasions with no etiology

revealed after workup contributes to almost 14.5% (2).Causes for PUO include infections, malignancies, inflammatory disease and miscellaneous.

We report a case of recurrent unexplained maternal fever during mid-trimester in two pregnancies, culminating in Intrauterine fetal demise (IUFD). A third pregnancy managed with early empirical immunomodulatory therapy resulted in a successful live birth.

CASE HISTORY

26yrs old G2P1L1, in a non-consanguineous marriage, presented at 23+2 weeks of gestation with fever of one week duration.

First Pregnancy

She had developed fever at 22 weeks' gestation. Details of evaluation are presented in **(Table 1)**. Her urinary tract infection was treated with antibiotics as per sensitivity, and repeat cultures were sterile. Abdominal ultrasound was normal. Despite treatment, fever persisted, and she had IUFD at 27 weeks. A stillborn male baby (700 g, small for gestational age) was delivered. Placental histopathology showed acute necrotizing villitis, while fetal autopsy was not performed. Fever subsided within three days postpartum.

Second Pregnancy

She again developed high grade fever at 22 weeks and admitted with us at 23 +2 weeks. At presentation: Pulse rate 125 bpm, Mean Arterial Pressure was 82 mmHg, temperature 102°f. She did not have any localising signs or symptoms nor a history of exposure. The investigations are detailed in **(Table 1)**. She was treated empirically with Ampicillin and later stepped up to Inj Meropenem when she developed hypotension. After discussion with obstetric medicine team, considering autoimmune etiology, started on parenteral steroids followed by oral prednisolone 30mg/day. She was afebrile for two days following parenteral steroids, but fever recurred on third day followed by IUFD at 25 weeks. She birthed a stillborn boy baby (620 grams, appropriate for gestation). Placenta weighed 235 grams, calcified **(Figure 1)**. Fever subsided within 24 hours of delivery. Placental membrane culture was sterile and histopathology was suggestive of Chorioamnionitis. Fetal autopsy was unremarkable. Chromosomal microarray revealed no pathogenic copy number variants.

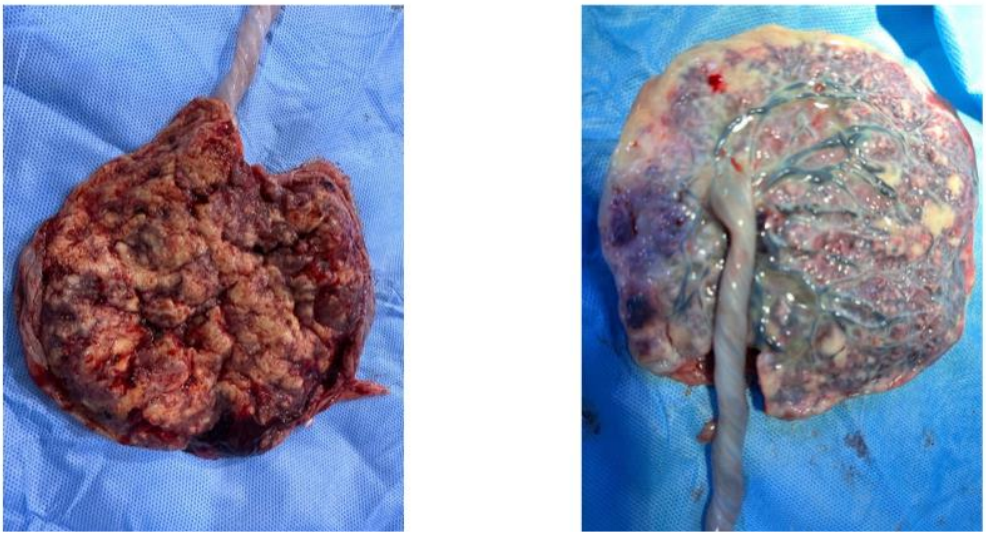

Figure 1: Image of the placenta after 2nd delivery which ended in IUFD

Table 1: Details of workup during the 1st and 2nd pregnancies -both ended in IUFD

	1st Pregnancy September 2022	2nd Pregnancy June 2023
Work up for Infectious Etiology		
Total Leucocyte count	24,290	10,500
Complete Urine examination		Normal
Smear for Malaria Parasite and Parasite F	Negative	Negative
Dengue NS1	Negative	Negative
High vaginal Swab		Sterile
Blood Culture:		no growth
Urine Culture	Klebsiella- treated; Repeat Culture -sterile	No growth
Lumbar puncture- Cerebrospinal Fluid evaluation		Normal
COVID-19 RTPCR		Negative
Listeria IgM		Negative
Scrub Typhus IgM	Negative	Negative
WIDAL	Negative	Negative
Brucella IgM	Negative	Negative
S. Procalcitonin:		Normal
Workup for Inflammatory markers		
C Reactive Protein		5.16 (0.0-0.5)
S. Ferritin		Normal
S. Triglycerides		Normal

LDH		Normal
ANA		Negative
c- ANCA	Negative	Negative
p-ANCA	Borderline positive	Negative
Imaging		
USG abdomen	Mild Hepatomegaly Mild Right Hydronephrosis	Normal
Chest X Ray PA view		Normal
2D echo normal	Normal	Normal
Others		
LFT, Creatinine		Normal

Evaluation in the interval period showed positive Lupus anticoagulant, and negative Anticardiolipin antibody, Beta 2 glycoprotein and screening for hereditary thrombophilia Couple Karyotype was normal. Autoimmune etiology or fetal allograft rejection was considered the most likely culprit.

Third Pregnancy and Outcome

Preconception counselling was done, and she conceived before repeat lupus anticoagulant testing. On confirmation of viability, she was started on azathioprine 50 mg twice daily, prednisolone 10 mg/day, aspirin 150 mg/day, and low-molecular-weight heparin 40 mg/day. She was closely monitored with blood counts, liver function, and urine cultures. Serial Fetal Growth scans showed an appropriately grown baby. At 29 weeks, she was diagnosed with intrahepatic cholestasis of pregnancy -total bile acids were 98µmol/L, with normal transaminases. She responded to ursodeoxycholic acid 300 mg TDS, and bile acids fell to 21µmol/L after two weeks. In view of early onset IHCP and previous history, labour was induced at 34 weeks. Emergency caesarean was done for cord presentation, delivered a baby girl 1950gms, 30th centile. Placenta weighed 350gms and histopathology showed appropriate villous maturation with no evidence of inflammation or villitis. Both mother and baby remained well at six-week follow-up

DISCUSSION

Early evaluation, identification and localization of the cause of fever in pregnancy is important to improve maternal and fetal outcomes. A comprehensive history and physical examination should include history of travel, medication/drug use, contact with animals and personal and family history of malignancies and inflammatory disorders. Evaluation of PUO is detailed in **(Figure 2)**.

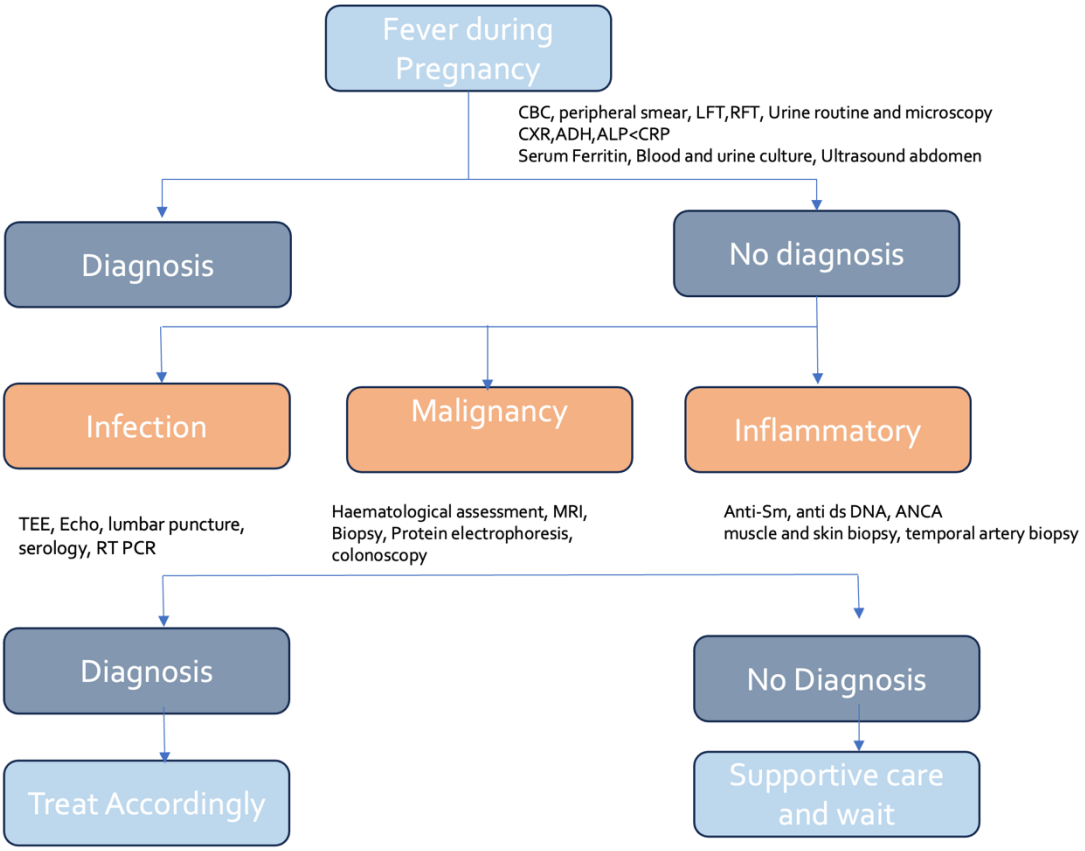

Figure 2. Workup for fever during pregnancy

(ADH: antidiuretic hormone; ALP: alkaline phosphatase; ANCA: antineutrophil cytoplasmic antibody; CBC: complete blood count; CRP: C reactive protein; CXR: Chest X ray; DNA: deoxyribonucleic acid; RFT: Renal function test; LFT: Liver function test; RT-PCR: reverse transcription polymerase chain reaction; TEE transesophageal echo cardiogram)

The adverse effects of fever on the fetus have been reported in various animal studies and case series [2]. The fetus and placenta are semi allografts to the mother. Fetal allograft rejection can manifest, in the extreme form, as intra uterine fetal demise, with the placenta showing features of chronic chorioamnionitis in the absence of amniotic fluid infection .In their study of placentas in cases of fetal deaths, Lannaman et al observed Chronic inflammatory lesions of the placenta in 57% of cases of fetal death after exclusion of infectious causes and also noted that amniotic fluid concentration of CXCL-10 (a chemokine elevated in transplant rejection) was significantly higher in patients with chronic inflammatory lesions than those without these lesions and propose that fetal demise can be caused by a breakdown of maternal-fetal tolerance [3].The placental histopathology in our case also showed features of necrotizing villitis in the first pregnancy and chorioamnionitis with negative culture for microorganisms in the second pregnancy, which could be a manifestation of allograft rejection.

Nardi E et al found significantly increased expression of placental interleukin 6, vascular endothelial growth factor receptor 2 mRNA, sphingosine 1-phosphate receptors and sphingosine kinase 2 in the placentas obtained after IUFD, whereas expression of activin A and of selected ATP binding cassette transporters is reduced, suggesting derangement in inflammatory and protective factors as the cause for fetal demise [4].

At present, confirmatory tests for fetal allograft rejection are in research stage, the treatment needs to be started on empirical basis after ruling out other causes for PUO and intrauterine fetal demise. This case highlights the need to think beyond infection when managing persistent fever in pregnancy. We initiated empirical immunosuppressive therapy in this mother early in her third pregnancy and we had a successful outcome. The woman did not develop pyrexia during her pregnancy and had a healthy baby.

CONCLUSION

Unexplained fetal demise can be a consequence of fetal allograft rejection and deranged inflammatory and protective factors. PUO in pregnancy may be a consequence of the same. We propose a role for empirical immunosuppressive therapy in selected cases for successful outcomes.

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