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Successful pregnancy outcomes following intravenous immunoglobulin treatment in a woman with a previous fetal death in utero due to gestational alloimmune liver disease: A case report

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ABSTRACT

Gestational alloimmune liver disease resulting in neonatal haemochromatosis is a rare but often lethal neonatal and fetal condition and is the leading cause of fetal and neonatal liver injury. Chelation-antioxidant treatment, intravenous immunoglobulin therapy and exchange transfusions, as well as liver transplantation have been used as treatments for the affected newborn at birth. In the reported case, a woman with previous neonatal death at 34 weeks of gestation due to gestational alloimmune liver disease commenced weekly doses of intravenous immunoglobulin (1 mg/kg) from 15 weeks in a subsequent pregnancy. A healthy baby boy was delivered following induction of labour at 36 weeks and 5 days of gestation. Following the same protocol, another healthy baby boy was delivered at 37 weeks of gestation. This case report emphasises the clinical utility of antenatal prophylaxis with intravenous immunoglobulin in women at high risk of recurrent gestational alloimmune liver disease.

1. Introduction

Gestational alloimmune liver disease (GALD) resulting in neonatal haemochromatosis (NH) is the leading cause of fetal and neonatal liver injury [1–4]. In GALD, a pregnant woman's immune system responds to a yet-to-be identified non-self fetal antigenic stimulus by producing immunoglobulin G (IgG) antibodies to fetal hepatocytes. These antibodies cross the placenta and bind to fetal hepatocytes, leading to their injury and death, resulting in fetal/neonatal cirrhosis and liver failure [1,2]. While it can cause fetal death in utero, most infants affected by this maternal-fetal alloimmune process are discovered to have liver failure shortly after birth and without effective treatment the prognosis is extremely poor [1]. Given its high recurrence rate, appropriate treatment and management of the subsequent pregnancies of a mother who has previously given birth to a baby with GALD-NH are essential for preventing the likely recurrence of this often-devastating condition [3].

2. Case Presentation

This is a case of a 32-year-old woman, gravida 3, now para 3 minus 1. Prior to the events described below, she had undergone a large loop excision of the transformation zone (LLETZ) for low-grade cervical intraepithelial neoplasia. Her follow-up cervical smears were normal. She also suffered with cold urticaria, for which she took regular antihistamines.

In her first pregnancy, following an uneventful antenatal course, she presented to her maternity hospital at 34 weeks of gestation with a 2-day history of reduced fetal movements. Ultrasound examination confirmed fetal death in utero and also demonstrated significant fetal ascites, together with pericardial, pleural and subcutaneous oedema. A stillborn male infant was delivered vaginally following induction of labour. An autopsy confirmed a hydropic male fetus with microscopic features of GALD, including extrahepatic siderosis.

Following this pregnancy loss, she went on to conceive the following year. Intravenous immunoglobulin (IVIg) at a dose of 1 mg/kg was commenced at 15 weeks of gestation. Serial fetal ultrasound scans in this pregnancy confirmed a well-grown fetus with normal amniotic fluid levels and umbilical artery Doppler findings, as well as no evidence of hydrops. She delivered a healthy, well grown baby boy at 36 weeks and 5 days of gestation following induction of labour.

Using the same IVIg treatment protocol, she also subsequently delivered another healthy baby boy at 37 weeks of gestation, again

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following an induction of labour. During this last pregnancy, she took 50 micrograms of thyroxine every second day for subclinical hypothyroidism in association with positive thyroid auto-antibodies. She was also noted to have an incidental lymphocytopaenia affecting all lymphocytic subsets but without any obvious clinical sequelae.

3. Discussion

NH is rare condition which occurs because of severe liver injury. It is the most common cause of acute liver failure in neonates [1–4]. Most cases are caused by GALD. Fetal growth restriction, prematurity and fetal death in utero are common in GALD-NH.

Given the rarity of GALD, as well as its often fatal outcome, prospective randomised control trials of treatment options are unlikely to ever be feasible. Evidence supportive of the efficacy of a particular treatment therefore requires comparisons with outcomes of historical cases. Chelation-antioxidant treatment, IVIg therapy and exchange transfusions, as well as liver transplantation have been used as treatments for the affected newborn, but with varying degrees of success [5–10]. Rodrigues et al. [5] concluded that chelation-antioxidant therapy in isolation did not improve the life expectancy of neonates with NH and that in their 19 examined cases, liver transplantation achieved the best long-term outcomes. Rand et al. [6] found that exchange transfusions and high doses of IVIg helped to avoid the need for liver transplantation. However, their follow-up time was on average only one year, which limits the strength of this conclusion. A more recent study published by Larson-Nath and Vitola [4] indicates liver transplantation remains an important treatment, particularly if less resource-intensive options prove unsatisfactory. These authors also stressed the importance of continuing research into GALD as one of the leading causes of neonatal acute liver failure, which still carries a significant mortality rate.

While its detailed mechanism of action is unclear, the beneficial impact of IVIg in GALD likely involves a combination of immunomodulatory, anti-inflammatory, and immune-protective effects, including inhibition of deleterious immune responses, influencing Fc expression on B lymphocytes, regulating apoptosis, and modulation of antigen-presenting cells [11].

Consensus guidance strongly suggests suspecting and testing for GALD-NH in any stillbirth to ensure early preventative treatment and management of the mother in future pregnancies given the high recurrence rate of GALD-NH in siblings [3]. Consequently, accurate diagnosis is imperative not only to minimise recurrence in affected women, but also to avoid missing other rare and fatal diseases in the differential diagnosis, such as galactosemia. Although supportive published data is scarce, preventative fetal treatment via the mother during pregnancy has been suggested as the most effective management of GALD [7,8]. The suggested prevention protocol is to administer IVIg, 1 g/kg weekly to a maximum dose of 100 mg, commencing between 14 and 18 weeks of gestation and continuing until delivery.

4. Conclusion

Improvements in managing neonates with GALD-NH have certainly occurred over the last two decades [4]. As proposed above, however, it is likely that the best treatment is prevention of future cases in women who have given birth to a baby with GALD. As a preliminary prerequisite to this approach, an accurate initial diagnosis is critical [3]. Starting early in the second trimester, this case supports the use of IVIg weekly in pregnancy to prevent this devastating neonatal condition. Given the unlikely feasibility of sufficiently powered prospective randomised trials of treatment and prevention options, this case report adds to the body of evidence necessary to optimise the clinical management of GALD. Future research that discovers the specific fetal antigen(s) responsible for the maternal-fetal alloimmune disease may allow the development of specific IgG prophylactic treatment similar to that which has been so successful in Rhesus isoimmunisation.

Contributors

Rebecca Moorhead contributed to case analysis, literature review, drafted the manuscript and approved the final version.

Jennifer Dean contributed to literature review, reviewed all drafts and approved the final version.

Shaun Brennecke was the senior clinician responsible for patient care, contributed to case analysis, drafting of the manuscript and approved the final version.

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Patient consent

Obtained from the patient.

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Conflict of interest statement

The authors declare that they have no conflict of interest regarding the publication of this case report.

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