Case report

A successful pregnancy after 8 consecutive miscarriages of a young woman with antisynthetase syndrome

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Abstract

Antisynthetase Syndrome is an autoimmune inflammatory condition which, due to its rarity, has not been well studied in pregnancy. The literature that does exist has shown affected patients are at significant risk of obstetric complications. We herein report the pregnancy of a 25-year-old gravida-9 para-0 woman who was referred to our regional obstetric unit at fifteen weeks gestation with her first ongoing pregnancy following eight previous first trimester losses. She had known Antisynthetase Syndrome with active disease at the time of conception. An ultrasound scan at 24+4 weeks gestation showed a fetus that was asymmetrically growth restricted with abnormal umbilical and middle cerebral artery dopplers. This triggered urgent transfer to a tertiary unit where she delivered a live baby male at 24+6 weeks gestation by classical caesarean section. The placenta showed evidence of maternal vascular malperfusion. Despite delivery at a periviable gestation her son is now four months of age. Reflecting on our own practice we present a management approach for future pregnancies with particular focus on fetal surveillance.

Introduction

The pregnancies of women affected by autoimmune connective tissue disorders provide challenges to their treating obstetric teams. These are high risk pregnancies and a multidisciplinary approach is necessitated. This report outlines the approach to antenatal care, leading to the delivery of a live infant, of a woman with Antisynthetase Syndrome who had suffered multiple previous pregnancy losses.

Antisynthetase Syndrome is an autoimmune idiopathic inflammatory condition characterised by the presence of autoantibodies against aminoacyl-tRNA synthases. It is very closely related to and often coexists with the inflammatory myopathies, dermatomyositis and polymyositis. Clinical features include rash, myositis, arthritis and alveolitis leading to interstitial lung disease. This lung disease is the hallmark of the condition and the cause of the most morbidity and mortality[1]. Immunomodulators are the mainstay of treatment, with corticosteroids generally used as first line agents[2].

It is a rare condition of which the exact incidence is unknown. Of the 2-10 new inflammatory myopathy

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cases per million each year, 20-40% will have associated antisynthetase antibodies[3]. Inflammatory myopathies, including Antisynthetase Syndrome affect women twice as commonly as men but only 14% of cases present during childbearing years[4]. As such, little is known about the progress of pregnancies in mothers affected by inflammatory myopathies and even less about those complicated by Antisynthetase Syndrome.

Case reports examining pregnancy outcomes in Antisynthetase Syndrome are sparse[5,6,8,9]. The pregnancies that are reported are associated with high rates of poor obstetric outcomes, especially when disease levels are high. We therefore wish to present this case as an example of obstetric management in a pregnancy complicated by Antisynthetase Syndrome with ongoing active disease.

Case presentation

A 25-year-old woman with Antisynthetase Syndrome was referred to our regional obstetric unit for management of her pregnancy. She was initially diagnosed with anti Jo-1 positive Antisynthetase Syndrome at age 19 following a presentation with joint pain, muscle weakness and rash. A muscle biopsy showed evidence of dermatomyositis and a chest CT scan showed bibasal interstitial lung disease. She was managed successfully with methotrexate for 2 years, achieving remission until it was discontinued due to the patient's desire for a pregnancy. Over the following years she suffered eight successive early miscarriages. These were all between 6- and 8-weeks' gestation and confirmed on ultrasound. Her antiphospholipid screen and thyroid function tests were normal. However, in 2019 she was found to have additionally developed anti-Ro antibodies.

Following cessation of methotrexate, she displayed ongoing clinical and biochemical evidence of disease activity despite treatment with multiple immunomodulatory agents including hydroxychloroquine, prednisolone, and regular intravenous immunoglobulin (IVIG, Intragam) infusions. She was reviewed multiple times by both Rheumatology and Obstetric Medicine for preconception counselling and was additionally commenced on low dose aspirin, folate, vitamin D and calcium. Enoxaparin was recommended but not started. With the introduction of tacrolimus at her final Rheumatology consultation prior to the confirmation of her pregnancy she had no overt weakness and her creatine kinase (CK) levels had decreased from 6972 U/L in September 2019 to 505 U/L in February of 2020.

In April 2020 she was reviewed in our antenatal clinic at 15+0 weeks gestation. This was her first pregnancy that had progressed past 8 weeks. Her weight was 62kg giving a body mass index of 21kg/m^2. Blood pressure was 110/60mmHg. Urinalysis was unremarkable.

An initial pregnancy ultrasound scan had been performed at 9+3 weeks gestation. Her aneuploidy screening at 12+5 weeks yielded a high risk first trimester combined screening result, showing a fetus with a 1:179 risk of trisomy 18 owing to an extremely low serum pregnancy-associated plasma protein A (PAPP-A) of 0.155 multiples of the median (MoM). Normal free beta human chorionic gonadotrophin and nuchal translucency were demonstrated. Invasive testing was declined.

Throughout her pregnancy she was regularly reviewed by the local Obstetric, Rheumatology, Obstetric Medicine and Midwifery teams. Her immunomodulatory agents were continued, and enoxaparin commenced. An ultrasound at 16+5 weeks gestation demonstrated a live fetus with an Estimated Fetal Weight (EFW) on the 67th centile for gestational age. At a subsequent detailed morphology ultrasound scan by Maternal Fetal Medicine at 20 weeks gestation, a fetus with an EFW on the 28th centile with no significant abnormalities was seen. A multidisciplinary plan was then put forward for two weekly ultrasound scans from 26 weeks gestation.

It was then decided to perform an additional routine ultrasound scan at 24 weeks in the context of the low PAPP-A and other risks associated with the pregnancy. The ultrasound scan at 24+4 weeks showed a fetus with severe asymmetric growth restriction. The EFW was 523g (<3rd centile), abdominal circumference (AC) was 181mm (<2nd centile), and head circumference (HC) was 223mm (37th centile). Normal fluid volume was observed. Umbilical Artery (UA) doppler showed increased resistance with absent end diastolic flow and the Middle Cerebral Artery (MCA) Pulsatility Index (PI) was low at 1.1 showing evidence of brain sparing. The Ductus Venosus (DV) waveform was slightly pulsatile with a positive A wave. The fetus had a heart rate of 171 beats per minute. However, the patient reported good fetal movements, denying abdominal pain, vaginal bleeding or fluid loss.

Following review of this scan she was urgently transferred from the community to our regional

hospital. On arrival a bedside ultrasound was performed showing a live fetus in breech presentation and an elevated Umbilical Artery Pulsatility Index was confirmed. A magnesium sulphate infusion was commenced and a dose of steroids (betamethasone 11.4 mg intramuscularly) given. She was immediately transferred to a tertiary obstetric unit where the fetus was closely monitored. Mother was seen by the neonatologists who counselled her regarding potential baby outcomes at 24+6 weeks gestation. However, mother was happy to take the risk of extreme prematurity, as she does not want to lose this baby. She developed abdominal pain in the early hours of the following morning (13 hours since the administration of betamethasone). The fetal heart rate monitoring showed deaccelerations. A live male infant weighing 582g was delivered by an emergency classical caesarean section. Cord gases revealed umbilical artery and vein pHs of 7.18 and 7.23 respectively which had justified the timing of delivery. Mother informed the authors that the baby is doing well at 6 months of age. Histopathological analysis of the placenta showed a small placenta <10th centile for gestational age with distal villous hyperplasia and increased peri-villous fibrin in keeping with maternal vascular malperfusion. Placental karyotyping showed no significant abnormalities.

The patient had an uncomplicated post-operative course and was discharged day 3 postpartum. She is not considering future pregnancies at this stage. The baby was admitted to the neonatal intensive care unit following delivery where he remained for one month before being discharged to the special care nursery. Despite an initial guarded prognosis he has survived to reach four months of age.

Discussion

Pregnancy presents a particular challenge for the clinicians responsible for a patient with Antisynthetase Syndrome. Given the complexity of these patients and their pregnancies a multidisciplinary approach to management is a necessity. Our discussion aims to explore the obstetric complications associated with Antisynthetase Syndrome, to understand the underlying mechanisms by which these occur and to propose an approach to fetal surveillance for future pregnancies.

A literature review of pregnancy in Antisynthetase Syndrome revealed four cases detailing five pregnancies [5,6,8,9]. Four of these resulted in live births however two of these were preterm deliveries (50%) and one (25%), like our own case, was at a periviable gestation of just 25 weeks. Both preterm deliveries occurred in women with evidence of active disease antenatally. In the case complicated by delivery at extreme prematurity, disease onset occurred at 5 weeks gestation. The patient was treated with high dose corticosteroids antenatally. Her weakness and respiratory symptoms markedly improved following this however extreme preterm delivery was necessitated due to severe early onset preeclampsia[5]. A Hungarian case report described a 20-year-old with anti Jo-1 Antisynthetase Syndrome who became pregnant 3 months after her diagnosis. She was treated with steroids but delivered a premature infant at 35 weeks gestation weighing only 1680g[6]. A reason for the premature delivery was not specified. This infant was likely growth restricted as this weight is <3rd centile for gestational age when compared to global data[7]. A second pregnancy was achieved but terminated on request[6]. Term deliveries following uncomplicated pregnancies were observed in two mothers who had achieved good disease control on immunomodulatory agents for years prior to conception[8,9]. These agents were continued antenatally. In one of these pregnancies reported by Green et al in 2018, calcium supplements and low dose aspirin 75mg were commenced from eleven weeks to reduce the risk of associated hypertensive disorders[8].

Although these reports detail only a small number of pregnancies it is clear that increased disease levels in Antisynthetase Syndrome are associated with increased adverse obstetric outcomes. The exact pathophysiological process by which this occurs is not well understood. It seems likely disease mediated microangiopathy leading to abnormal placental formation and function plays a role in the development of complications. Placental dysfunction has been implicated in the development of a plethora of obstetric issues including pregnancy loss, preterm birth, intrauterine growth restriction and hypertensive complications. In our own case there was overwhelming clinical and histopathological evidence of placental malperfusion leading to a hypoxic fetal state. Massive perivillous fibrin deposition on placental histopathology, as was seen in our case, is strongly associated with placental mediated disorders[10]. This phenomenon has been reported in case reports examining inflammatory myopathies. It is postulated, in this setting, that the placental villous invasion may be a T cell mediated process due to the common features between synctiotrophoblastic cells and skeletal muscles[11]. Whatever the cause, the effects on developing pregnancies can be devastating.

Appropriate fetal surveillance is key to the successful management of a pregnancy in the setting of Antisynthetase Syndrome. In our own case, the severe fetal compromise was only detected sonographically. Clinically the patient felt well and reported normal fetal movements. As evidenced by the literature review, patients with Antisynthetase Syndrome are at significant risk of developing obstetric complications related to placental malperfusion. Disease mediated perivillous fibrin deposition causes a reduction of the surface area for fetoplacental blood and nutrient exchange, leading to an increase in placental blood flow resistance. This is reflected in increased umbilical artery resistance and an elevated Pulsatility Index on Doppler flow. Absent end diastolic flow on umbilical artery Doppler, as seen in our own case, generally does not occur until 60-70% of the villous vascular tree has been compromised posing significant risk of fetal hypoxaemia[12]. There are no clear guidelines to suggest ultrasound frequency to monitor fetal growth and the development of placental dysfunction. As it is evident pregnancies in the setting of active disease are at risk of delivery at extreme prematurity it might be prudent to suggest that pregnancies complicated by Antisynthetase Syndrome have regular weekly ultrasounds including Doppler studies from 23-24 weeks gestation to monitor for early onset growth restriction. In the setting of disease quiescence, serial ultrasonography in the third trimester monitoring growth and umbilical artery dopplers should be recommended.

A further complicating factor in this particular case was the presence of anti-Ro antibodies. While commonly found in patients with Antisynthetase Syndrome these are not unique to the condition. Significantly, they are associated with a 1-2% risk of fetal congenital heart block and hence require additional fetal surveillance protocols. If these antibodies are present, local practice is to perform fetal heart rate monitoring weekly from 16 weeks and four weekly ultrasound growth and wellbeing. A tertiary morphology scan is recommended. If this is not possible a fetal echocardiogram should be performed instead. As always, in addition to the above measures it is essential to continue regular best practice obstetric care and monitoring.

This case has been an interesting opportunity for our institutions to reflect on our management of these medically complicated pregnancies and we hope this discussion can help other units going forward. Ultimately at the time that the 24+4-week ultrasound was assessed, the poor fetal condition was correctly identified and transfer to a tertiary unit for delivery was swiftly organised. Timely steroids and fetal neuroprotection with magnesium sulphate were given. Although it can be a difficult decision to deliver on the threshold of viability the umbilical cord gases reflect our decision to transfer was well founded. Despite his extreme prematurity the infant has survived to four months of age. Due to his gestation at birth he is at risk of developing multiple medical complications throughout his life including chronic lung disease, severe visual impairment, hearing impairment, cerebral palsy, and cognitive developmental delay[13]. However, this was a woman who was determined to be a mother and had already suffered eight successive pregnancy losses, a live born delivery was therefore a desired outcome.

Summary

- Antisynthetase Syndrome is a rare condition and therefore associated pregnancy is uncommon. When it does occur, it is associated with multiple obstetric complications such as increased pregnancy loss, hypertensive disorders of pregnancy, preterm birth and intrauterine growth restriction.
- The exact mechanism of pregnancy complications is unknown, but it is likely related to autoimmune mediated microangiopathy leading to placental malperfusion and fetal hypoxia.
- Regular weekly fetal monitoring through ultrasound should be considered from 23-24 weeks gestation in the setting of active disease to monitor for placental dysfunction.
- Multidisciplinary and multispecialty care is imperative to ensure the best possible outcome for mother and baby.

Data availability

Readers could access the data supporting the conclusions of the case report by contacting the corresponding author either by email or in writing.

Conflict of interest

All authors have no conflict of interest to declare.

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