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Ballantyne syndrome: A review on a rare condition of pregnancy

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ABSTRACT

Mirror syndrome, also known as Ballantyne syndrome, is a rare pregnancy condition characterized by the presence of the clinical triad of fetal hydrops, placentomegaly, and maternal edema. Fetal hydrops can be caused by any etiology, including rhesus iso-immunization, congenital infection, twin-to-twin transfusion, structural anomalies, and fetal malignancies. Although the pathogenesis is unknown, it appears to be similar to trophoblastic damage and maternal vascular endothelial dysfunction seen in pre-eclampsia, and thus the two conditions may have a similar clinical presentation. They may even coexist in cases where a patient with maternal mirror syndrome develops pre-eclampsia-like symptoms. To prevent fetal mortality and maternal morbidity, a timely, accurate diagnosis and prompt interventions are required.

REVIEW ARTICLE

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INTRODUCTION

Mirror syndrome (MS), also known as Ballantyne syndrome or triple edema, is characterized by the presence of a clinical triad of hydrops of the fetus, placenta, and mother. John William Ballantyne first described this rare condition in 1892, with the original theory being that rhesus iso-immunization of the fetus was the cause of maternal hydrops. [1] O'Driscoll described a similar case in 1956, and the term "mirror syndrome" was coined because the mother's edema mirrors that of her fetus and placenta.

However, as recent literature describes, with the advent of ultrasound and prenatal diagnosis, the current thought is that multiple aetiologies causing severe hydrops fetalis, that is, both immune and non-immune hydrops, can lead to maternal mirror syndrome. [3]

Although the pathophysiologic mechanism of this rare syndrome is unknown, a recent report suggested that a functional alteration in the placenta similar to that seen in pre-eclampsia may be involved [4]. Maternal hypertension and edema are common manifestations of both disease entities [4].

The available literature suggests that mirror syndrome can be distinguished from pre-eclampsia by its earlier onset in pregnancy, the absence of hyperreflexia, and the presence of hemodilution (anemia and hypoalbuminemia), which contrasts sharply with the hemoconcentration seen in pre-eclampsia patients.

Features of Ballantyne syndrome

Mirror syndrome was thought to be caused by rhesus isoimmunization before 1970 [1]. However, with the advent of ultrasound and prenatal diagnosis, it became clear that a variety of etiologies could eventually result in severe hydrops fetalis, similar to that seen in mirror syndrome [5]. The authors of a 2006 study proposed that placental edema with secondary placental hypoxia could be the initial event [6]. The placenta's role in the

etiology of mirror syndrome cannot be overstated.

The role of the placenta in the etiology of mirror syndrome cannot be overlooked. Multiple placental factors have been associated with mirror syndrome, including fms-like tyrosine kinase 1 (sFlt-1), placental growth factor (PlGF), and B-HCG [7]. Recent reports suggest that an increased amount of the placental factor sFlt-1 and decreased PIGF expression is strongly associated with mirror syndrome [7.8]. However, the same pattern of changes was also noted in patients with pre-eclampsia [7]. To solve this puzzle, De Olivera et al. in 2011, demonstrated that the ratio of sFlt-1: PIGF of > 85 favors a diagnosis of pre-eclampsia [9]. He hypothesized that mirror syndrome patients have higher PIGF levels due to an increased placental mass and therefore, exhibit lower ratios [9]. Mirror syndrome usually manifests between 16 and 34 weeks of gestation [10]. Affected mothers usually present with edema, weight gain, hypertension, elevated liver enzymes, anemia, headache and visual disturbance. Upon further investigation, a fetal ultrasound typically shows the presence of hydrops fetalis and/or placental edema [10]. In addition, rhesus isoimmunization, multiple pregnancies, viral infections, fetal malformations, and placental and fetal tumors have been noted in some cases of mirror syndrome [10]. Twin-to-twin transfusion syndrome [7] and leukemia [11] have also been reported in association with mirror syndrome.

A wide range of treatment modalities have been utilized to reverse the maternal symptoms and to improve fetal hydrops [6, 10]. However, no comparison between the effects of these different modalities on fetal and maternal outcomes has been provided in the current literature. When fetal hydrops is irreversible, induction or termination of the pregnancy may be the only choice to ensure the safety of the mother. A complete reversal of maternal symptoms usually occurs following delivery or termination [6]. The prognosis of patients with mirror syndrome is generally characterized by increased maternal morbidity and fetal mortality. The currently reported rate of intrauterine fetal death is 56% [6].

Clinical features of Ballantyne syndrome

The clinical syndrome of Ballantyne syndrome or Mirror syndrome (MS) could be well understood by a clinical case study. A case study on Ballantyne syndrome or Mirror syndrome (MS) helps us to get a better insight on this rare embryological complication.

A 28-year-old healthy woman of South-East Asian ethnicity was booked into the hospital's antenatal clinic early in the first trimester. The pregnancy had been progressing well. The patient had had one pregnancy 5 years prior, which was a rare abdominal pregnancy in the pouch of Douglas, finally resulting in a laparotomy, termination of pregnancy (fetal size of approximately 13 weeks) and salpingectomy. The patient was known to be a carrier of the alpha thalassemia trait and her partner's screen was negative.

At her first-trimester antenatal screen, she was noted to be Rhesus positive, negative for HIV, hepatitis B, hepatitis C and syphilis. She was also found to be rubella immune. Her combined first-trimester screen was reported as low risk for trisomy 21, 18 and 13.

The 15-week visit was routine. Her blood pressure was noted to be within the normal range (around 110/70 mmHg), the uterus appeared adequate for dates and an ultrasound scan revealed an active fetus of normal appearance. The next follow-up visit would be in 3 weeks.

However, at 17 weeks 3 days gestation, the patient presented to the emergency department with swelling in both legs. The patient's blood pressure was 144/92 mmHg, with grade 3 pitting pedal oedema up to mid-thigh in both legs. The patient reported mild frontal headache but no blurring of vision or right upper quadrant pain. She also reported a weight gain of 10 kg over 2 weeks. She denied any febrile episodes, history of rash, lower abdominal pain or bleeding per vaginum. Bilateral deep patellar reflexes were brisk but no ankle clonus was demonstrated.

Ultrasound examination revealed fetal death in utero (FDIU) with the bi-parietal diameter corresponding to 16 weeks and 4 days of gestation. There was evidence of

gross fetal hydrops with severe ascites, skin oedema and pleural effusion. The urine dipstick revealed 1+ of nitrite-free protein with a protein/creatinine ratio (PCR) of 22 mg/mmol. The B-hCG was >200,000 IU/L, likely due to placental edema. All FDIU investigations were requested, including toxoplasmosis, cytomegalovirus and parvovirus B19 serology screen. The patient's blood pressure remained within the higher limits of normal, at 130–140/80–90 mmHg. Subsequently, labor was induced with a mifepristone-misoprostol regimen. The patient delivered a stillborn female, weighing 127 g. The placenta was pale and on histopathology was noted to have oedematous and immature villous maturation. As the patient's blood pressure remained within normal limits and she was well, she was discharged home on day 1 post-delivery with a clinic follow–up scheduled for 2 weeks. Subsequently, maternal parvovirus B19 serology was reported to be positive for IgM antibodies, which confirmed congenital parvovirus infection to be the cause of fetal hydrops.

On day 3 post-delivery, the patient presented to the emergency department with increasing dyspnoea, worsening since discharge and now present on rest. She reported chest tightness and left-sided chest pain radiating into the neck with a worsening of frontal headache. She also reported worsening of upper and lower limb swelling, as well as facial puffiness. She denied any febrile episodes, cough, right upper quadrant pain, any visual symptoms or lower abdominal pain. Her heart rate was 65 beats per minute, her blood pressure was 190/90 mmHg and her oxygen saturation was 99% on room air. However, the patient was in tripod position, and appeared uncomfortable and distressed; her respiratory rate was 35 breaths per minute. Grade 2 pitting edema was elicited in the upper limbs up to the elbows and there was persistent grade 3 pitting edema up to mid-thigh in the lower limbs. On auscultation, air entry was noted to be reduced in bilateral lung basal lobes, though, with no evidence of crepitations or wheeze. Both heart sounds were audible, with no evidence of murmur. Bilateral patellar tendons revealed hyperreflexia with two beats of ankle clonus bilaterally.

Troponins were significantly elevated, at 234 ng/L. The urine dipstick now revealed 2+ of nitrite-free protein with a PCR of 31 mg/mmol. The urine output was noted to be 30 ml/h during the initial investigation. A chest X-ray revealed bilateral lower lobe pleural effusion and evidence of pulmonary edema. Transthoracic echocardiography revealed normal biventricular size, normal valvular function and a normal left ventricle with an ejection fraction of 65%. However, a small pericardial effusion was noted (possibly explaining the rise in troponin level). There was no evidence of dilated right ventricle or right heart strain and a computed tomography pulmonary angiogram was negative for pulmonary embolism.

The patient was admitted to the intensive care unit with an unclear diagnosis and multi-system supportive therapy was commenced. She was administered intravenous hydralazine initially for blood pressure control. She was also commenced on intravenous magnesium sulphate (MgSO4) because of features of atypical severe pre-eclampsia. Several other differential diagnoses were considered, including peripartum cardiomyopathy and cardiac failure because of severe dyspnoea; hence, calcium channel blockers and beta-blockers were avoided. Intravenous frusemide was commenced with caution given interstitial fluid overload, despite the differential of pre-eclampsia at this stage, as the hematocrit revealed an expanded rather than a contracted intravascular volume. In retrospect, the diagnosis of mirror syndrome was made because of the presence of fetal hydrops, maternal anasarca, mild hypertension and maternal haemodilution, which then progressed to severe pre-eclampsia with worsening hypertension, proteinuria, hyperreflexia and persistence of maternal edema after delivery, which in the scenario of mirror syndrome alone should have resolved with delivery. Similarly, although pre-eclampsia has been thought to resolve with delivery, it can present in the postpartum period of an uneventful pregnancy, but why this occurs is not fully understood. The patient

made a substantial recovery over the next 24–48 h, with decreasing need for supplemental oxygen, normalizing respiratory rate, decreasing edema and improving biochemical markers. By day 6 post-delivery (day 3 of admission), the patient reported that she experienced almost no dyspnoea on mobilization and that her limb swelling had reduced by over 75%. She was discharged on day 4 of admission on a tapering regimen of low-dose anti-hypertensives for blood pressure control and diuretic therapy was ceased. At her follow-up visit a week later, she reported being well. Her blood pressure was well within normal limits and no maternal edema was elicited.

Diagnosis of Ballantyne syndrome

The diagnosis of mirror syndrome relies primarily on the simultaneous identification of both fetal and maternal findings. However, this pattern of concomitant presentation is not always present. Fetal findings may predate maternal findings by 1–2 weeks and vice versa. Knowledge regarding these patterns of presentation could improve the diagnostic accuracy of practicing physicians to obtain a differentiated diagnosis from other related conditions such as pre-eclampsia. It can also help identify patients suspected to develop mirror syndrome and thus, implement frequent surveillance to facilitate early detection. However, when statistically analyzed, whether fetal and maternal presentations were simultaneous or on different dates does not affect fetal mortality (Mann-Whitney U test, P-value = 0.46). Thus, the order of presentation of symptoms in mothers and fetuses alone, without considering the treatment, is not helpful to predict the outcome

Treatment of Ballantyne syndrome

Throughout the cases we reviewed, maternal conditions consistently improved once the fetal hydrops was corrected. According to a center-based study that was published in 2015, Hirata et al. noted, in one patient known to have mirror syndrome, that an invasive intervention improved the fetal condition and maintained the pregnancy of that patient [12]. In concordance, after correlating the effect of different treatment modalities with fetal outcomes, we found that procedural interventions to correct the fetal hydrops/anemia (32/113, 28.3%) were significantly associated with improved fetal survival ($\chi 2$ test, P = 0.01). In addition, induction of labor (14/113, 12.40%) was also associated with a similar survival benefit (Fisher's exact test, P = 0.02). This sort of statistical correlation between the interventions and the outcomes was not provided on the previous literature concerning mirror syndrome.

Prognosis of Ballantyne syndrome

The fetal prognosis in mirror syndrome is generally poor. The overall mortality rate identified in our study was 76/113, 67.26%. Intrauterine fetal death comprised 44/76, 57.89% of mortalities and 44/113, 38.9% of all cases. This is compared to the previous systematic review, which reported an intrauterine fetal death rate of 35.7% of all cases [13]. Neonatal death accounted for (26/76, 34.21%) of mortalities. It should be noted that mirror syndrome appears to have no impact on maternal mortality, as no case has been reported. After delivery or termination of the pregnancy, the median time needed for maternal recovery was 5.5 days (IQR = 8 days). In contrast, the meantime to maternal recovery in a previous study was 8.9 days [13]. This discrepancy could be attributed to increased physician's awareness about this rare condition over time; which facilitates an earlier detection and improved patient care. It might be also a random variation.

CONCLUSION

As the one of the systematic reviews to statistically correlate the therapeutic interventions with fetal outcome, we found here that the implementation of a procedural intervention to correct fetal hydrops/anemia was significantly associated with improved fetal survival. The induction of labor also provided a similar survival benefit. However, the applicability of such invasive interventions should be carefully considered; to avoid the potential harm caused by these procedures. The gestational age at diagnosis and sequence of presentation have an insignificant impact on fetal outcome. Isoimmunization and perinatal infections, albeit previously associated with

mirror syndrome, are uncommon associations. Further studies are warranted to investigate the role of the placenta, and placental factors in the pathogenesis of mirror syndrome as the currently available data are insufficient to reach a meaningful conclusion.

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