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A Role of the Anti-angiogenic Factor sVEGFR-1 in the “Mirror Syndrome” (Ballantyne’s Syndrome)

Jimmy Espinoza^{1,2}, Roberto Romero^{1,3}, Jyk Kae Nien¹, Juan Pedro Kusanovic¹, Karina Richani¹, Ricardo Gomez⁴, Chong Jai Kim^{1,5}, Pooja Mittal², Francesca Gotsch¹, Offer Erez¹, Tinnakorn Chaiworapongsa², Sonia Hassan^{1,2}

¹Perinatology Research Branch, NICHD/NIH/DHHS, Bethesda, Maryland, and Detroit, Michigan, USA;

²Department of Obstetrics and Gynecology, Wayne State University/Hutzel Women’s Hospital, Detroit, Michigan, USA;

³Center for Molecular Medicine and Genetics, Wayne State University, Detroit, Michigan, USA;

⁴CEDIP, Department of Obstetrics and Gynecology, Sotero del Rio Hospital, Puente Alto, Chile;

⁵Department of Pathology, Wayne State University/Hutzel Women’s Hospital, Detroit, Michigan, USA.

Abstract

Background: “Mirror Syndrome” (Ballantyne’s Syndrome) refers to the association of fetal hydrops with placentomegaly and severe maternal edema. Preeclampsia occurs in approximately 50% of the cases. Soluble vascular endothelial growth factor receptor-1 (sVEGFR-1), an anti-angiogenic factor, has been implicated in the pathophysiology of preeclampsia (PE).

Objective: The objective of this study was to determine if the maternal plasma concentration of sVEGFR-1 is elevated in patients with “Mirror Syndrome”.

Study Design: This case-control study included patients with uncomplicated pregnancies (n=40) and patients with “Mirror Syndrome” (n=4) matched for gestational age. “Mirror Syndrome” was defined as fetal hydrops and severe maternal edema. Maternal plasma sVEGFR-1 concentrations were determined using specific ELISA. Immunohistochemistry of sVEGFR-1 on villous trophoblasts was also performed in samples from one patient with “Mirror Syndrome” and compared with those from a patient with spontaneous preterm delivery matched by gestational age. Non-parametric statistics were used for analysis ($p < 0.05$).

Results: 1) The median maternal plasma concentration of sVEGFR-1 was significantly higher in patients with “Mirror Syndrome” than in the control group (median: 3,974 pg/mL, range: 3,083–10,780 vs. median: 824 pg/mL, range: 260–4712, respectively; $p < 0.001$); and 2) all patients with “Mirror Syndrome” had sVEGFR-1 concentrations above the 95th percentile for gestational age. Syncytiotrophoblast, especially syncytial knots, showed strong staining with antibodies against

sVEGFR-1 in placental samples from the patient with “Mirror Syndrome”, but not in those from the patient with spontaneous preterm delivery.

Conclusion: High maternal plasma concentrations of sVEGFR-1 were observed in “Mirror Syndrome”. We propose that this anti-angiogenic factor may participate in the pathophysiology of this syndrome. Thus, maternal plasma determination of sVEGFR-1 may help to identify the hypoxic fetus that places the mother at risk for preeclampsia.

Keywords

mirror syndrome; Ballantyne’s syndrome; sVEGFR-1; preeclampsia; villous edema

INTRODUCTION

More than 100 years ago, John H. Ballantyne used the term “general dropsy of the fetus” to refer to fetal hydrops and concomitant edema of the placenta. Moreover, he reported that marked maternal edema and uterine distention were observed far more commonly with hydrops fetalis than in normal fetuses, and that albuminuria was associated with maternal edema in these cases [1]. The term “Mirror Syndrome” was introduced by O’Driscoll in 1956, who reported that in cases of fetal hydrops, “the mother to some degree mirrors the edema of the fetus” [2]. Ballantyne’s Syndrome was initially reported in cases of rhesus isoimmunization [2–7]. However, it has since been described as well in other pregnancy complications associated with fetal hydrops including: cytomegalovirus [8] and Parvovirus B 19 [9] infections, Ebstein’s anomaly [10], aneurysm of the vein of Galen [11], fetal supraventricular tachycardia [12], and placental chorioangioma [13].

“Mirror Syndrome” is also referred to as pseudotoxemia; however, hypertension and proteinuria consistent with the clinical diagnosis of preeclampsia is present in about half of the cases of “Mirror Syndrome” [1–16]. Recently, the soluble vascular endothelial growth factor receptor-1 (sVEGFR-1), an antiangiogenic factor, has been associated with the pathogenesis of preeclampsia [17–19]. Thus, the objective of this study was to determine if the maternal plasma concentration of sVEGFR-1 is elevated among patients with “Mirror Syndrome”.

MATERIAL AND METHODS

Study design:

This case-control study included patients with “Mirror Syndrome” (n=4) and gestational age-matched controls (n=40). “Mirror Syndrome” was defined as fetal hydrops and severe maternal edema [1,2]. Preeclampsia was diagnosed in the presence of systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg on at least two occasions, 4 hours to 1 week apart, and proteinuria (≥ 300 mg in a 24-hour urine collection or one dipstick measurement $\geq 2+$). Severe preeclampsia was defined as severe hypertension (diastolic blood pressure ≥ 110 mmHg) plus mild proteinuria, or mild hypertension plus severe proteinuria (a 24-hour urine sample containing ≥ 5 g protein or urine specimen $\geq 3+$ protein by dipstick measurement). Patients with an abnormal liver function test (aspartate aminotransferase >70 IU/L) plus thrombocytopenia (platelet count $<100,000/\text{cm}^3$) were also classified as having

severe preeclampsia. Control cases consisted of patients who had a normal pregnancy and delivered a neonate that was appropriate for gestational age. These patients were matched for gestational age with the “Mirror Syndrome” cases.

All women provided written informed consent prior to the collection of plasma samples. The collection and utilization of the samples was approved for research purposes by the Institutional Review Board of the National Institutes of Child Health and Human Development.

Sample collection and human sVEGFR-1 immunoassay:

Venipuncture was performed and the blood was collected into tubes containing EDTA. The samples were centrifuged at 4°C for 10 minutes and stored at -70°C until assay. The concentrations of sVEGFR-1 were measured using a commercially available enzyme-linked immunosorbent assay (ELISA) as previously described [18]. The inter- and intra-assay coefficients of variation (CVs) for human sVEGFR-1 immunoassay in our laboratory were 4.8% and 6.9%, respectively. The sensitivity of the assay was 17.8 pg/mL.

Histological examination:

Placental samples for histological examination were available in one patient with “Mirror Syndrome”. The histological findings were compared with that from a patient with spontaneous preterm delivery matched by gestational age. Immunohistochemistry of sVEGFR-1 on villous trophoblasts was also performed in the samples from the patient with “Mirror Syndrome”. Deparaffination of 5- μ m-thick tissue slides, rehydration, and antigen retrieval were followed by immunohistochemistry using an automatic immunostainer (Ventana Discovery, Ventana Medical Systems, Inc., Tucson, AZ). Antigen retrieval was performed using Proteinase 2 solution for 8 minutes. Sections were treated with 10% normal horse blocking serum for 20 minutes. Subsequently, sections were incubated with primary antibody (1:300 in dilution, polyclonal goat anti-VEGF-R1, R&D Systems, Minneapolis, MN). Biotin-conjugated horse anti-goat antibody (1:200 in dilution, Jackson Immuno Research Laboratories, Inc., West Grove, PA) was applied as the secondary antibody. A DAB MAP kit (Ventana Medical Systems Inc., Tucson, AZ) was used for staining and Hematoxylin was used as a counter stain. A blocking peptide (1:25, R&D Systems, Minneapolis, MN) mixed with the primary antibody was used as a negative control.

Statistical analysis:

Plasma sVEGFR-1 concentrations were not normally distributed; therefore, non-parametric statistics were used for analysis. The 5th and 95th percentiles for the maternal plasma concentration of sVEGFR-1 were calculated for each gestational age in the normal cases, and the plasma concentrations of sVEGFR-1 of the four “Mirror Syndrome” cases were compared to the normal values. The statistical package used was SPSS v.12.0 (SPSS Inc., Chicago, IL). A p-value <0.05 was considered significant.

RESULTS

The clinical characteristics of the patients with “Mirror Syndrome” are displayed in Table I. One patient developed preeclampsia five weeks after sample collection, the other three patients had preeclampsia at the time of sample collection. One of these patients developed eclampsia during labor. All four cases delivered before 35 weeks of gestation.

The median maternal plasma concentration of sVEGFR-1 was significantly higher in patients with “Mirror Syndrome” than that of women in the control group (median: 3,974 pg/mL, range: 3083–10,780 vs. median: 824 pg/mL, range: 260–4712, respectively; $p < 0.001$). All patients with “Mirror Syndrome” had sVEGFR-1 concentrations above the 95th percentile for gestational age (Figure 1).

Histological examination of the placenta in a case of “Mirror Syndrome” revealed immature intermediate villi with edematous changes (Figure 2a), increased syncytial knots, increased intervillous fibrin, and multifocal villous calcifications (Figure 2b). In contrast, histological examination of the placenta, in the case with spontaneous preterm delivery without “Mirror Syndrome”, did not show these histological findings (Figure 2c). Syncytiotrophoblast, especially syncytial knots, showed strong staining with antibodies against sVEGFR-1 in the placental samples from the patient with “Mirror Syndrome” (Figure 3a and 3B), but not in those from the patient with spontaneous preterm delivery (Figure 3c).

DISCUSSION

Principal finding of this study:

“Mirror Syndrome” is associated with a high maternal plasma concentration of sVEGFR-1.

A role for the fetus:

“Mirror Syndrome” is characterized by the combination of fetal hydrops and severe maternal edema. Hypertension and proteinuria consistent with the clinical diagnosis of preeclampsia has been described in approximately half of the cases of “Mirror Syndrome” reported thus far (Table II). The observations that preeclampsia associated with “Mirror Syndrome” can resolve after the treatment of fetal anemia with an intrauterine transfusion in cases of Parvovirus B19 infection [9], correction of severe fetal tachycardia [12], or following the death of the hydropic fetus in twin pregnancies [14,16] indicates that the fetus plays an important role in the pathogenesis of “Mirror Syndrome”.

Preeclampsia as an anti-angiogenic state:

Accumulating clinical and experimental evidence indicates that a subset of mothers with preeclampsia and/or SGA fetuses has an anti-angiogenic state. The following observations support this view: 1) serum from pregnant women with preeclampsia has anti-angiogenic properties demonstrated in the tube-formation assay [17]; 2) high maternal plasma concentrations of sVEGFR-1, a potent anti-angiogenic agent, have been reported at the time of the diagnosis [17–19] and before the development of preeclampsia [19,20]; sVEGFR-1 binds to the free form of vascular endothelial growth factor (VEGF) and placental growth factor (PIGF) reducing their bioavailability and their pro-angiogenic effect [17,21]; 3)

VEGFR-1 mRNA is upregulated in placentas from preeclamptic patients [17]; 4) patients with preeclampsia have lower concentrations of PlGF and free VEGF than normal pregnant women [17,21]; and 5) the administration of adenovirus, expressing the sVEGFR-1 gene, to pregnant animals induces the clinical presentation of preeclampsia [17]. Collectively, this evidence indicates that sVEGFR-1 participates in the pathophysiology of preeclampsia. It seems that not all women with preeclampsia have elevated anti-angiogenic factors or low concentrations of angiogenic cytokines (free VEGF, PlGF, or angiogenin, among others). Moreover, an anti-angiogenic state is not specific to preeclampsia, because mothers with small-for-gestational-age fetuses (SGA) also have higher median maternal plasma concentrations of sVEGFR-1 than patients with normal pregnancy [18], but lower than patients with preeclampsia. This finding suggests that an anti-angiogenic state during pregnancy has a broad spectrum of severity ranging from mild to severe and that it can be expressed with different phenotypes: SGA [18], fetal death of unknown etiology, and preeclampsia. Of interest, other obstetrical syndromes, such as preterm labor and preterm rupture of membranes, are not characterized by an elevation of the maternal plasma concentration of sVEGFR-1 (unpublished observations).

Why do mothers of fetuses with hydrops develop edema and/or preeclampsia?

Hydrops is frequently a manifestation of fetal cardiac failure [22] and is associated with villous edema [1]. This condition is characterized by high intracellular water content and high total placental water [23]. Compression of the villous blood vessels by edematous villi or a thicker interface may impair oxygen exchange [24,25]; the greater the severity of villous edema, the lower the umbilical artery cord pH [25]. It has also been proposed that edematous villi may reduce the intervillous space and the intervillous blood flow with subsequent reduction in the fetal oxygen supply [26].

We propose that hypoxia of the villous trophoblast in cases of villous edema leads to increased production and release of sVEGFR-1 (and, perhaps, other anti-angiogenic factors) into the maternal circulation. Excessive concentrations of these products would then be responsible for maternal edema in “Mirror Syndrome” and for the endothelial cell dysfunction in those cases complicated with preeclampsia. Evidence in support of this includes: 1) cytotrophoblast [27] and trophoblast cells [28] cultured under hypoxic conditions upregulate the mRNA expression and production of sVEGFR-1 in the supernatant; and 2) the observations of the current study, in which the maternal plasma concentrations of sVEGFR-1 are increased in mothers with “Mirror Syndrome”.

Why do some mothers with hydropic fetuses develop “Mirror Syndrome” and others do not?

The excessive production of anti-angiogenic factors may be a function of the severity of the villous edema, as well as the genetic factors responsible for the production, metabolism and functional control of pro- and anti-angiogenic factors. Some mothers may be more susceptible than others to a given concentration of anti-angiogenic factors.

Two distinct placental lesions (hypoperfusion and villous edema), preeclampsia, and sVEGFR-1

The placental lesions frequently associated with preeclampsia include maternal abnormalities (failure of physiologic transformation of the spiral arteries, acute atherosclerosis, thrombosis or decidual necrosis) [29,30] and fetal abnormalities (intervillous thrombi, localized ischemic villous necrosis, thrombotic occlusion of the fetal stem villous artery and decreased number of terminal villi) [29,30], which have been characterized as reflecting placental hypoperfusion. Yet, in “Mirror Syndrome”, the cardinal histologic finding is villous edema. We interpret this as indicating that two different pathologic processes lead to the development of a maternal anti-angiogenic state and the syndrome of preeclampsia. This suggests that the syndrome has a common pathway that includes the development of an anti-angiogenic state. A limitation of this study is that placental samples were available only from one case of “Mirror Syndrome”.

Further studies

Longitudinal studies of mothers with hydropic fetuses who develop “Mirror Syndrome” with and without preeclampsia are required to characterize the profile of pro-angiogenic and anti-angiogenic factors. Moreover, serial observations in patients in whom “Mirror Syndrome” resolves spontaneously after fetal treatment or the death of a hydropic co-twin can provide insights into the mechanism of disease. We welcome the opportunity to collaborate with investigators with appropriately collected samples with informed consent and IRB approval to address these issues.

Conclusion

We propose that maternal edema and preeclampsia in cases of fetal hydrops is the result of an anti-angiogenic state.

Acknowledgments

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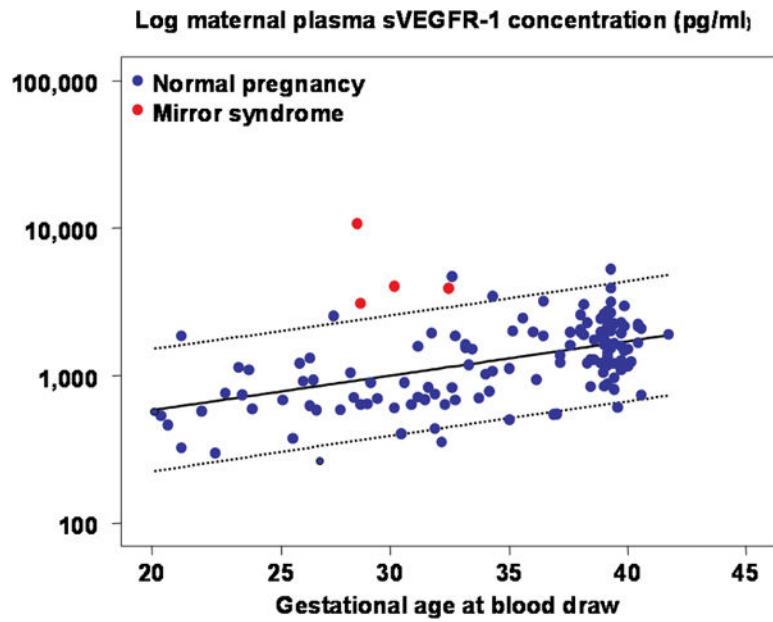


Figure 1. Maternal plasma concentration of sVEGFR-1 in patients with “Mirror Syndrome” and in those with uncomplicated pregnancies. The lower and upper lines represent the 5th and 95th percentiles of the plasma sVEGFR-1 concentrations among patients with normal pregnancies.

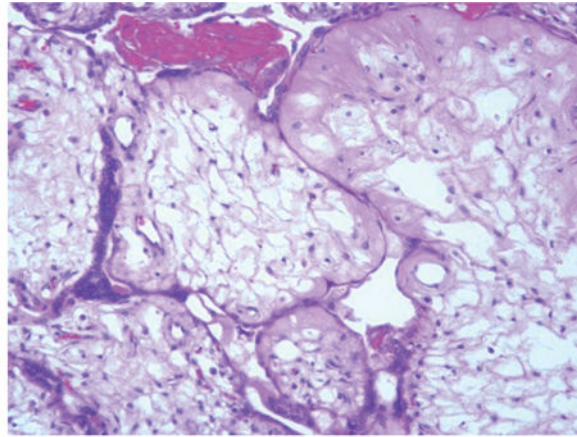
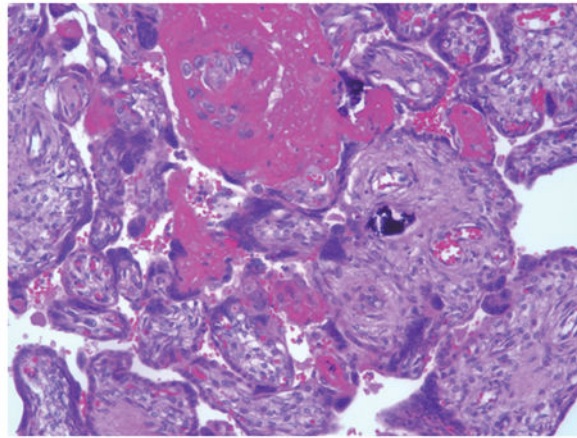
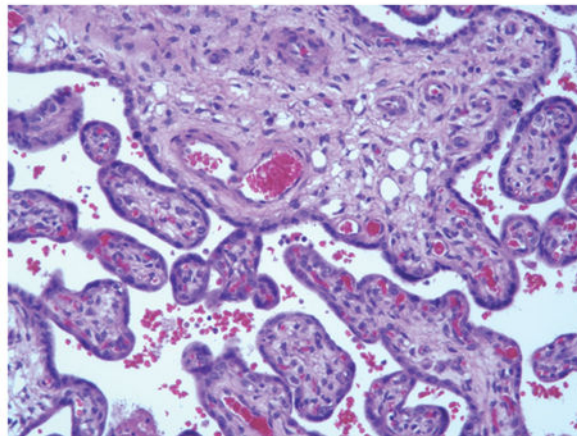
2a**2b****2c**

Figure 2. Histological examination of placental samples with Hematoxylin and Eosin (H&E) demonstrated immature intermediate villi with edematous changes (Figure 2a) and increased syncytial knots, increased intervillous fibrin, and multifocal villous calcifications (Figure 2b). In contrast, examination of the placental samples from the spontaneous delivery case did not show these histological findings (Figure 2c).

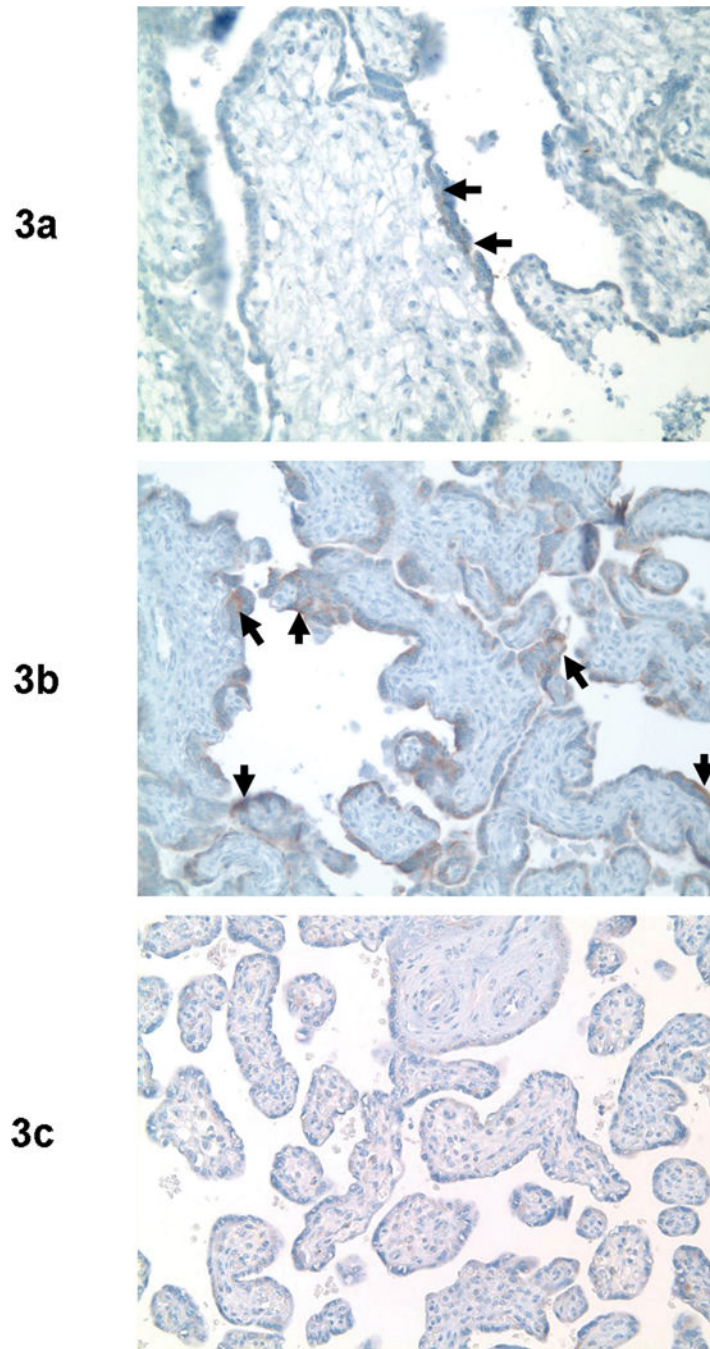


Figure 3. Syncytiotrophoblast, especially syncytial knots, showed strong staining with antibodies against sVEGFR-1 in the placental samples from a patient with “Mirror Syndrome” (Figure 3a and 3B), but not in those from the patient with spontaneous preterm delivery (Figure 3c).

Table 1.

Clinical characteristics of the patients with “Mirror Syndrome”

Cases	GA at blood draw (weeks)	GA at diagnosis of PE (weeks)	sVEGFR-1 plasma concentration (pg/mL)	GA at delivery (weeks)	Birthweight (g)	Main diagnosis
1	28.6	28.6	10,780,000	28.6	1080	Non-immune hydrops fetalis, eclampsia
2	28.7	34.1	3,083,640	34.1	2340	Non-immune hydrops fetalis, severe PE
3	32.4	32.4	3,912,658	34.0	3380	Non-immune hydrops fetalis, PE, multiple fetal anomalies
4	30.1	30.1	4,037,571	30.1	2190	Rh (-) isoimmunization, polyhydramnios, gestational diabetes, severe PE

GA: gestational age, PE: preeclampsia, sVEGFR-1: soluble vascular endothelial growth factor receptor-1

Table II.

Summary of the reports of “Mirror Syndrome” cases

Author (s)	Cases (#)	GA at diagnosis (weeks)	Diagnosis	Highest BP	Proteinuria	Peripheral edema	Placentomegaly	Comments
Ordóñez SA et al[11]	1	30	Aneurysm of the vein of Galen	140/100	3.5 grms/24 hrs	4+	yes	Resolved after intrauterine transfusion
Duthie SJ et al[9]	1	25	Parvovirus B19 infection	165/100	8.5 grams/24 hrs	None reported	yes	IUFD
Quagliarello et al[8]	1	30	Cytomegalovirus infection	140/100	1.3 grms/24 hrs	Gross pitting edema	yes	Resolved after selective feticide
Heyborne KD et al[14]	1	16	Twins discordant for fetal hydrops	147/80	1+	Peripheral edema	not reported	Resolved after spontaneous fetal demise
Pirhonen JP et al[16]	1	28	Twins discordant for fetal hydrops	130/90	1+	Marked edema	Grossly hydropic in the affected twin	
Vidaeff AC et al[15]	1	31	Severe fetal ascitis	136/64	not reported	Yes	not reported	
Midgley DY et al[12]	1	27	Supraventricular tachycardia	130/90	0.89 gr/24 hrs	Yes	not reported	Resolved following flecainide treatment
O'Driscoll DT et al[2]	3	32–36	RH isoimmunization	130/90	no	Yes	yes	Perinatal death
Cohen AI[3]	1	29	RH isoimmunization	140/90	not reported	Yes	yes	IUFD
John AH et al[6]	20	28–40	RH isoimmunization	140/90 or more	65% (13/20)	85% (17/20)	yes	IUFD or perinatal death
Scott JS[7]	26	not reported	RH isoimmunization molar pregnancy	140/90 or more	yes	yes	yes	
Hirsch MR et al[5]	1	28	RH isoimmunization	130/80	4+	Yes	yes	IUFD
Goodlin RC[4]	10	32–34	RH isoimmunization	40% (4/10) had BP 140/90	40% (4/10) had 1+ or more	Yes	not reported	IUFD in all cases
Kaiser IH[1]	1	not reported	Lung sequestration	140/90	59 mg/24 hrs	Yes	Placental weight: 1,020 grams	Perinatal death
Dorman SL et al[13]	1	19	Placental chorioangioma	220/126	4+	Gross pitting edema	Placental chorioangioma	Termination of pregnancy
Carbillon, L. et al[10]	1	31	Ebstein's anomaly	180/110	not reported	Edema of the face and hands	Grossly edematous	Stillborn