Case report: a novel approach to prevent chronic histiocytic intervillositis and recurrent pregnancy loss by targeting maternal alloimmunity

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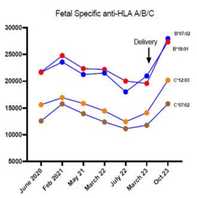
BACKGROUND Recurrent miscarriage is a distressing condition with limited therapeutic options. Chronic histiocytic intervillositis of unknown etiology (CIUE) is a rare inflammatory placental disorder characterized by maternal immune cell infiltration of the intervillous space, fibrin deposition, and ischemic tissue damage, leading to pregnancy loss. The condition likely reflects an immune response against paternal alloantigens, with histopathological features resembling antibody-mediated rejection in solid organ transplantation.

AIM We investigated two women with recurrent CIUE-related pregnancy losses. Detailed immunological profiling included anti-human leukocyte antigen (HLA) antibody characterization, compatibility testing, and histopathological examination of previous placentas, as well as screening for other causes of recurrent pregnancy losses. Based on evidence of antibody-mediated alloimmune injury, we implemented a targeted immunosuppressive regimen derived from transplantation medicine, combining intravenous immunoglobulins (IVIG), tacrolimus, corticosteroids, and hydroxychloroquine, with close pregnancy monitoring.

CONCLUSION These cases support the concept that CIUE represents a breakdown of maternal immune tolerance toward paternal antigens, mediated by fetal-specific anti-HLA antibodies—akin to solid organ graft rejection. An immunosuppressive protocol adapted from transplantation medicine achieved two successful live births after multiple CIUE-related pregnancy losses. Targeting antibody-mediated alloimmunity may represent a promising therapeutic strategy for selected patients with recurrent miscarriage due to CIUE. Further studies are warranted to define optimal regimens and identify predictors of response.

Year of conception	Trialed medication	Week of gestation at pregnancy loss	Placenta/fetal tissue analysis after pregnancy loss
2017	None	17+6/7	Early intrauterine fetal growth restriction. Massive chronic intervillositis with increase in peri-villous fibrin deposition.
2018	None	11+6/7	Massive chronic intervillositis with increase in peri-villous fibrin deposition.
2018	*From pregnancy diagnosis onward* Aspirin 100 mg/d Hydroxychloroquine 200 mg/d Prednisone 10 mg/d	6+3/7	Very little materiel, showing intervillous cellular deposition and highly positive for HLA-DR staining, indicative of immune-mediated pathogenesis.
2019	*Preconceptionally* Aspirin 100 mg/d Hydroxychloroquine 200 mg/d Prednisone 20 mg/d *Additional from pregnancy diagnosis (6 WG) onward* Pravastatin 10 mg/d Enoxaparin 40 mg/d	8+3/7	NA
2019	*Preconceptionally* Aspirin 100 mg/d Hydroxychloroquine 400 mg/d Prednisone 20 mg/d *Additional from pregnancy diagnosis (6 WG) onward* Pravastatin 10 mg/d Enoxaparin 40 mg/d	7+2/7	NA
2020	*From pregnancy diagnosis (6 WG) onward* Aspirin 100 mg/d Prednisone 5 mg/d Tacrolimus (through level 6-8 ng/ml)	8	NA

HLA Loci group	Patient		First Child (1st Husband)		2nd Husband		Mismatch Load (to 2nd Husband)
A/B/C	A*26:01 **B*27:05** C*02:02	A*02:07 **B*44:02** C*05:01	A*26:01 **B*27:05** C*02:02	A*33:01 **B*58:01** C*04:01	A*03:01 **B*07:02** C*07:02	A*25:01 **B*18:01** C*12:03	N=39 Eplets
DR81/3/4/5	DRB1*04:04 DRB4:01:03	DRB1*13:01 DRB3*01:01	DRB1*04:04 DRB4:01:03	DRB1*01:02 Absent	DRB1*04:04 DRB4*01:03	DRB1*15:01 DRB5*01:01	N=11 Eplets
DQA1/DQB1	DQB1*03:02 DQA1*03:01	DQB1*06:03 DQA1*01:03	DQB1*03:02 DQA1*03:01	DQB1*05:01 DQA1*01:01	DQB1*03:02 DQA1*03:03	DQB1*06:02 DQA1*01:02	N=9 Eplets
DPA1/DPB1	DPB1*02:01	DPB1*04:01	DPB1*02:01	DPB1*03:01	DPB1*04:01	DPB1*06:01	N=4 Eplets

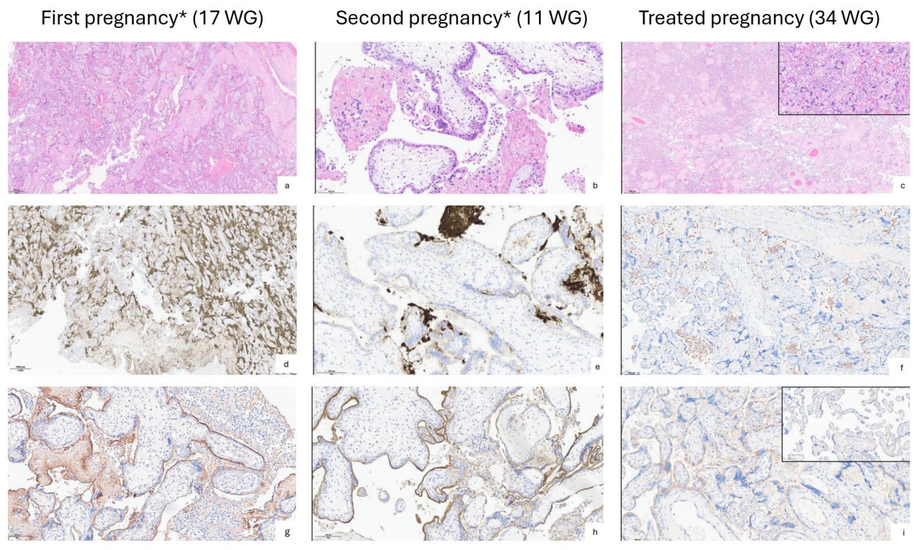


HLA: A/B/C Mismatch details: 39 Eplets position

28 Predicted and [11Antibody verified]

All mismatches: 9D, 24S, 30G, 44RT, 62QE, 63NI, 66IY, 69RA, [70IAQ], 71QS, [71TS], 73AS, 76ES, 76ESI, **[76ESN], [76VRN],** 76VS, 77S, 77SRN, [80I], **[80N],** 97I, 97S, 97W, 99S, 113H, 113HD, 114R, [144KR], 147L, 152A, 152RA, [161D], 170RH, 177DK, [180E], [193PL], [267QE], 275EL

Single Allele mismatch load:
A*03:01 (7) A*25:01(4) B*07:02(14) B*18:01(13) C*07:02 (15) C*12:03 (8)

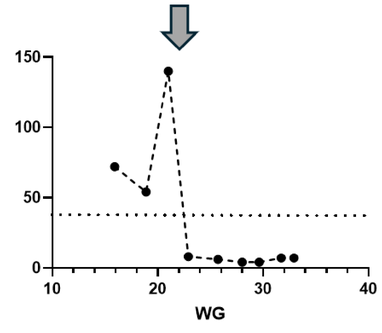


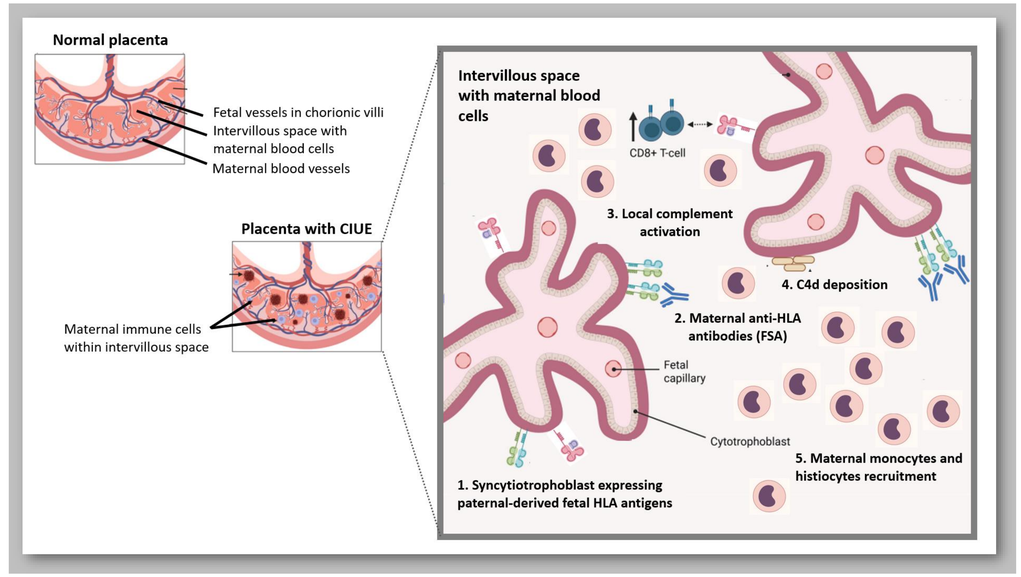
Protocol intensification:
- IVIG **weekly** infusion
+ Oral prednisolone 10 mg PO once daily
+ Azathioprine 1mg/kg/day PO once daily
+ Prophylactic low molecular weight heparin

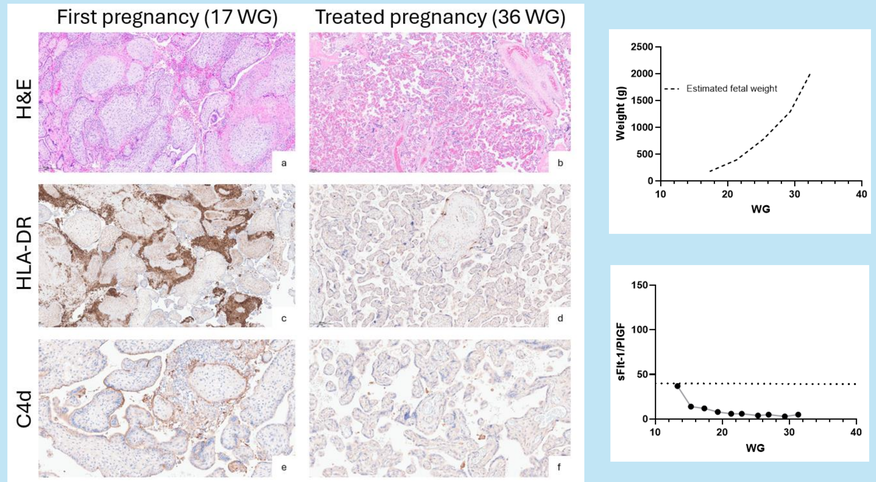
Pre-conception phase and early pregnancy phase:
- Intravenous immunoglobulins (IVIG) 2g/kg monthly
- Methylprednisolone 1 mg/kg IV bolus with each IVIG infusion
- Tacrolimus PO BID for trough levels 6-8 ng/ml
- Aspirin 100 mg PO once daily
- Hydroxychloroquine PO BID 5mg/kg/day

Start ≥12 weeks prior to conception attempt

Maternal surveillance: Tacrolimus through level 3 weekly until steady state then monthly; BP, renal function, electrolytes and glucose profile at each visit.
Fetal surveillance: Ultrasound and sFlt-1/PlGF ratio in maternal serum, bi-monthly from 16 WG onward







METHOD The first patient, after six consecutive CIUE-related pregnancy losses, underwent preconception desensitization and continued treatment throughout pregnancy. Early signs of placental dysfunction prompted therapy intensification, leading to delivery of a viable infant at 33+2 weeks. Placental histology showed only minor residual CIUE lesions. The second patient, with two pregnancy losses and a fetal demise from CIUE, began treatment at 6 weeks' gestation and delivered a healthy infant at 36 weeks. In both cases, therapy was generally well tolerated, with gestational diabetes as the main complication, and no major maternal or neonatal adverse events.

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