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Original Research Article

Placental pathology in maternal autoimmune diseases-new insights and clinical implications

Ramya T.^{1*}, Umamaheswari G.², Chaitra V.²

¹Department of Obstetrics and Gynecology, ²Department of Pathology, PSG Institute of Medical Sciences and Research, Coimbatore, Tamil Nadu, India

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***Correspondence:**

Dr. Ramya T.,

E-mail: ramya.t2003@gmail.com

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ABSTRACT

Background: Pregnancy in women with autoimmune diseases is frequently associated with placental insufficiency leading to adverse perinatal outcome. Aim of the study was to investigate the presence and possible clinical significance of placental lesions in mothers with different autoimmune disorders.

Methods: In this retrospective study, 11 placentas from 10 mothers with diverse autoimmune diseases including systemic lupus Erythematosus (SLE), antiphospholipid antibodies (APLA), idiopathic thrombocytopenic purpura (ITP) and antinuclear antibodies (ANA) were studied.

Results: Placental correlates were reduced placental weight, maternal vascular under perfusion, abruption, villitis of unknown etiology, multifocal chorangiomas, distal villous immaturity, massive perivillous fibrin deposition/maternal floor infarction and foetal thrombotic vasculopathy. Of the 11 pregnancies 3 were untreated (1 SLE, 2 APLA) and resulted in intrauterine foetal demise. The lesions were more severe in these cases. All the treated pregnancies resulted in live born babies (8), of which 3 were growth restricted, 2 were complicated with oligohydramnios and 3 were delivered preterm.

Conclusions: In this group of diverse autoimmune disorders, placental lesions were not specific for each of them. Apart from maternal vascular under perfusion, lesions like villitis of unknown etiology, distal villous immaturity and massive perivillous fibrin deposition were identified and may recur in subsequent pregnancies and treatment should be directed towards modifying it. The placental examination should be mandatory in all cases of maternal autoimmunity and pregnancies with poor foetal outcome.

Keywords: Maternal autoimmune diseases, Maternal vascular under perfusion, Placental lesions

INTRODUCTION

Placenta plays a major role for a pregnancy to proceed normally, ensuring an adequate blood supply to support and promote the growth of the developing foetus. Autoimmune disease, both organ specific and non-organ specific is associated with intrauterine growth retardation (IUGR), preterm delivery and intrauterine foetal demise (IUFD) and appears to be a consequence of failure of the

normal uterine physiologic changes to occur with resultant placental insufficiency and the features that accompany a failing placenta.¹ Despite being an important etiology of poor perinatal outcome, placental lesions and its clinical correlation of autoimmune diseases lack a unified diagnostic criterion.

These clinical associations as well as foetal outcome suggest that there may be multiple pathologies that

complicate and disrupt pregnancy in patients with autoimmune disorders.²

Given these uncertainties surrounding the placental pathology of autoimmune diseases, we sought to determine the presence and possible clinical significance of maternal vascular lesions, chronic villitis of unknown etiology (VUE), distal villous immaturity (DVI), massive perivillous fibrin deposition/maternal floor infarction (MPVFD/MFI) in placentas of mothers with different autoimmune disorders.

METHODS

This retrospective study was carried out from January 2014 to April 2017 in the Departments of Obstetrics and Gynecology and Department of Pathology at PSG IMS and R.

A total of 11 placentas were studied from ten mothers with maternal immunological disorders which included systemic lupus erythematosus (SLE) with secondary anti phospholipid antibodies (APLA), primary anti phospholipid antibodies (APLA), idiopathic thrombocytopenic purpura (ITP) and one with antinuclear antibody (ANA).

All patients had singleton pregnancies without any foetal malformations. Infants below tenth percentile were considered as having intrauterine growth restriction.

According to the revised sydney classification criteria, apla is defined by

- Presence of lupus anticoagulant (LA) in plasma on two or more occasions at least 12 weeks apart
- Presence of moderate to high levels of anticardiolipin (aCL) (IgG or IgM) in serum or plasma (i.e., >40 IgG phospholipid units (GPL)/mL or IgM phospholipid units (MPL)/mL or >99th percentile) on two or more occasions at least 12 weeks apart
- Presence of moderate to high levels of anti-beta-2 glycoprotein I antibodies (IgG or IgM) in serum or plasma (> 99th percentile) on two or more occasions at least 12 weeks apart.²

Patients with SLE were diagnosed according to the American Rheumatism Association Diagnostic Criteria.² Both patients with ITP were diagnosed during the pre-pregnancy period.⁴

An entire placenta was available from all 10 patients and were fixed in 10% formalin. Placentas were weighed after the membranes and umbilical cord were trimmed off and compared with the reference weights for trimmed singleton placentas. Two rolls of membranes were taken and umbilical cord was examined for length, diameter, colour, insertion site and number of twists.⁵ Photography of the placentas were routinely taken after examining foetal and maternal surfaces.

The placentas were cut at 1cm intervals and the parenchyma was assessed for colour, sponginess and specific lesions. Relevant lesional sections were taken along with membrane roll, cord and normal parenchyma. All the histologic sections were stained with hematoxylin and eosin.

RESULTS

Over a period of 3-years 11 placentas from 10 mothers with the clinical and laboratory evidence of maternal autoimmune diseases were included in the study.

Two out of ten studied patients had SLE with secondary APLA, five had primary APLA, two had ITP and one with ANA positivity. One patient with ITP had two consecutive pregnancies and both placentas were studied

Patients with SLE

Clinical data and placental findings from the two studied patients with SLE are shown in Table 1. Both of our patients had SLE with secondary APLA.

Patient 1 was diagnosed 9 years before the index pregnancy. Her first pregnancy was an induced abortion owing to SLE flare, while the second was a spontaneous abortion. She had active renal involvement and superimposed preeclampsia in the present pregnancy. She was treated with low molecular weight heparin (LMWH), immunomodulators, anti-hypertensives and aspirin. She delivered a preterm small for gestational age (SGA) baby at 34 weeks of gestation due to preterm premature rupture of membranes (PPROM). Her placenta was small with thin hypercoiled cord (8 twists for 11.0cms of cord length-). Microscopically it showed maternal vascular underperfusion which included distal villous hypoplasia, increased syncytial knots, abundant perivillous fibrin deposition and calcification. Multifocal chorangiomas (Figure 1) was also noted.

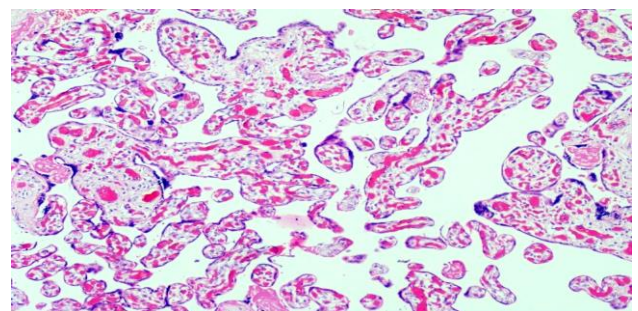


Figure 1: Multifocal chorangiomas-immature intermediate villi with proliferating capillaries and surrounding pericytes (H and E, 4X).

Patient 2 was a second gravida with previous spontaneous abortion at 8 weeks. Now she was referred with an intrauterine foetal demise at 24 weeks of gestation. On evaluation she was found to have malar rash,

thrombocytopenia and presence of anti Sm antibodies. On investigating further, she also had an abnormal lupus anticoagulant (LA), with elevated titres of anticardiolipin (aCL) antibody IgG and beta 2 glycoprotein 1 IgM.

The placenta was very small (less than 10th percentile) and had thin, flat umbilical cord. The parenchyma grossly showed marginal atrophy and a basal firm yellow nodule.

Microscopically, some of the chorionic plate and stem villous vessels showed recanalizing thrombi and haemorrhagic endovasculitis (foetal thrombotic vasculopathy). There was laminar necrosis of the decidua, patchy lymphohistiocytic villitis, intervillitis (Figure 2), microinfarcts and foci of avascular, hyalinized villi. Basal haematoma with indentation of parenchyma was also noted.

Table 1: Patients with SLE.

Details	Patient-1	Patient-2
Maternal age	27	21
autoimmune etiology	SLE (Class 4 lupus nephritis), secondary APLA, hypothyroidism	SLE with secondary APLA
Duration since diagnosis	9 years	Post -partum
Laboratory data	aCL IgM, IgG positive, anti-ds DNA positive	ANA positive (Sm positive, nucleosome positive), Abnormal LA, aCL IgG positive, anti-beta 2 glycoprotein 1 IgM positive, Thrombocytopenia
Previous obstetric history	G1-MTP at 8weeks due to SLE flare G2-spontaneous abortion at 18 weeks G3-PP	G1-Spontaneous abortion at 8weeks G2-PP
Gestational age at delivery	34W+1D	24W+1D
Course during pregnancy/complications	Superimposed preeclampsia, IUGR, PPRM	Malar rash
Treatment during pregnancy	LMWH, antihypertensives, Aspirin, Steroids, immunomodulators and eltroxin	None
Foetal outcome	SGA, Live birth	IUFD
Foetal weight	1.4 kg	150gms
Gross		
Placental weight	*194.0gms (<10 th percentile)	*19.0gms (<10 th percentile) *Thin, flat cord
Cord	*Thin, hypercoiled cord	Basal firm yellow nodule, at the level of cord insertion
Any specific lesions	*Small subchorionic haemorrhage	Marginal atrophy and basal haematoma
Microscopy	Maternal vascular underperfusion (Distal villous hypoplasia, Increased syncytial knots, Abundant perivillous fibrin deposition and calcification)	Thrombi, infarcts Recanalizing thrombi and haemorrhagic endovasculitis of stem villous vessels, avascular hyalinized villi (Foetal thrombotic vasculopathy)
	Multifocal chorangiomas	Retroplacental haematoma Villitis and perivillitis Laminar necrosis of the decidua

Patients with APLA

Clinical data and placental findings from the five studied patients with primary antiphospholipid antibodies are shown in Table 2. In patients 4 and 6, presence of APLA were diagnosed postpartum and the pregnancies resulted in intrauterine foetal demise. In the remaining three patients two were diagnosed even before attempting the studied pregnancies and were treated optimally which resulted in live births. Patient 3 was diagnosed to have

APLA at the end of first trimester. She was tested during the ongoing pregnancy as she had previously delivered a premature, growth restricted baby with absent diastolic flow in umbilical artery doppler. Two out of the 3 live births were appropriate for gestational age (AGA). Of the three treated patients two were delivered near term, while the third (patient 3) was preterm.

In four out of 5 patients, the placental weight was small for gestational age. The placenta of the three live born

fetuses showed maternal vascular under perfusion (infarcts, intervillous thrombi and decidual vasculopathy) and vascular ectasia with hypercapillarization.

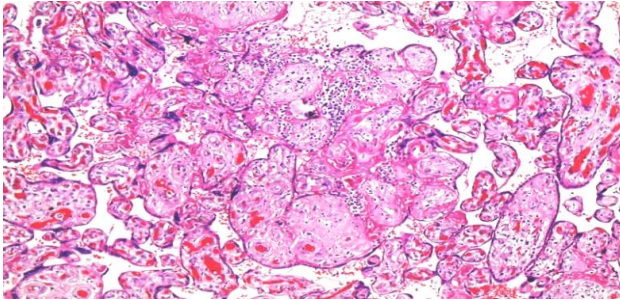


Figure 2: Lymphohistiocytic infiltrate in VUE (H and E, 10X).

Placenta of patient 6 (IUGR) showed retroplacental haematoma with parenchymal indentation, subchorionic haematoma and intervillous thrombus. Interestingly the other IUGR (patient 4) had a AGA stillbirth and her placenta showed distal villous immaturity (Figure 3).

There were patchy, multifocal chorangiomas and villous stromal karyorrhexis. Lowgrade, focal villitis of unknown etiology was also noted.

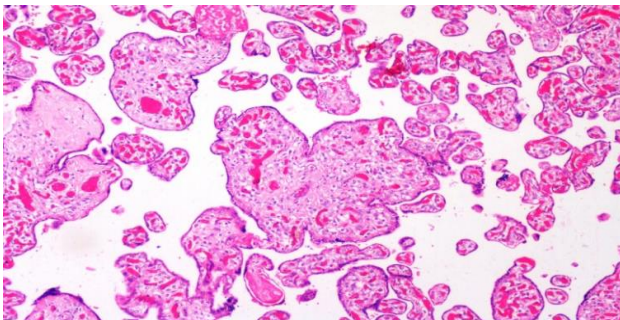


Figure 3: Distal villous immaturity- immature villi with irregular outlines, paucity of vasculosyncytial membranes (H and E, 10X).

Patients with ITP

Clinical data and placental findings from the 3 studied pregnancies with idiopathic thrombocytopenic purpura are shown in Table 3.

Patient 9 had two successive pregnancies that were studied. Both the pregnancies were complicated by oligohydramnios. She had active disease during her first pregnancy and was treated with immunoglobulins, steroids and multiple transfusions. None of the babies were SGA or stillborn.

Almost all the placentas were $\leq 10^{\text{th}}$ percentile. Maternal vascular underperfusion was found in 2 placentas of the three studied pregnancies (patient 8 and 9B) with ITP.

Hypercoiling of the cord and haemorrhage around the umbilical vessels were present in patient 9B.

Transmural massive perivillous fibrin deposition (maternal floor infarction) was noted in patient 9A (Figure 4). Intervillous thrombi and lymphocytic deciduitis were also identified.

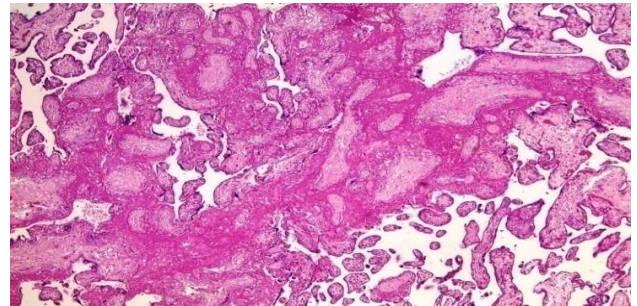


Figure 4: Massive perivillous fibrin deposition-marked increase in transmural perivillous fibrin deposition involving >50% of the villi.

Patient with ANA

Clinical data and placental findings of the patient with antinuclear antibody is shown in Table 3.

Patient 10 was a low risk primigravida and on routine screening was found to have high resistance flow in uterine artery at mid trimester. On screening for autoimmunity she tested positive for antinuclear antibodies. She was treated with LMWH from 20 weeks and delivered a SGA baby at near term.

Placenta showed both maternal vascular under perfusion and foetal thrombotic vasculopathy which was evident by infarcts, distal villous hypoplasia, hypercapillarization, increased syncytial knots and fibrin thrombi of chorionic plate and stem villous vessels with large foci of avascular hyalinized villi (more than two foci/average of 15 or more affected villi/slide/ foetal vessel lesions) (Figure 5).^{6,7}

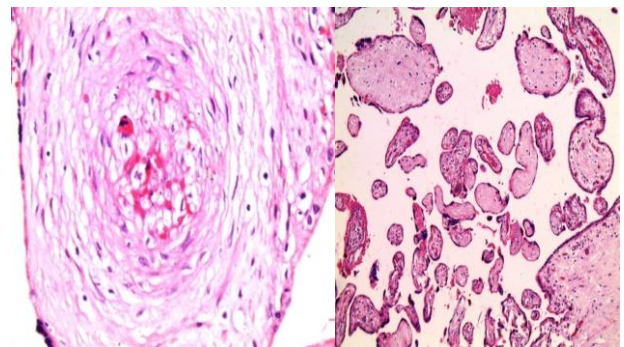


Figure 5: Foetal thrombotic vasculopathy-A) Stem villi with recanalizing thrombus B) groups of avascular hyalinized villi, >15 villi.

Table 2: Patients with antiphospholipid antibodies.

Details	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Maternal age	24 Years	23 years	19years	22years	28 years
Autoimmune etiology	APLA	APLA, Overt hypothyroidism	APLA	APLA	APLA, old cerebral venous thrombosis
Duration since diagnosis	First trimester of PP	Post-partum of present pregnancy	1 year (post abortal)	Post-partum (present pregnancy)	9 years
Laboratory data	aCL IgM positive	Anti-beta 2 glycoprotein 1 IgG positive	aCL IgM positive	Abnormal LA, aCL IgG Positive, anti beta 2 glycoprotein1 IgG and IgM positive	Abnormal LA, aCL IgG positive
Previous obstetric history	G1-emergency LSCS at 35 weeks (IUGR, AEDF) G2-MTP at 8 weeks G3-PP	G1-Spontaneous abortion at 20weeks G2-PP	G1-missed abortion G2-missed abortion G3-PP	Primi	G1-normal vaginal delivery(treated)
Gestational age at delivery	33W+2D	38 W+5D	36weeks	32W+6D	37 W+3D
Course during pregnancy/ complications	Subclinical hypothyroidism, GGI	Cervical encirclage done at 13 weeks (history indicated)	GGI	Grade 3 abruption	None
Treatment during pregnancy	Aspirin 75mg from 10 weeks UFH from 12 weeks, steroids for lung maturity	Eltroxin	LMWH from 12 weeks	None	LMWH from 12 weeks
Foetal outcome	AGA, Live birth	IUFD	AGA, Live birth	IUFD	SGA, Live birth
Foetal weight	1.8 kg	3.4KG	2.75 kg	1.7 kg	2.44kg
Gross					
Placental weight	307.0gms	389.0 gms (<10 th percentile)	445.0gms	271.0gms (<10 th percentile)	345.0gms (<10 th percentile)
Cord	Marginally inserted hypercoiled cord	Edematous hypocoiled cord	Eccentrically placed	Hypocoiled cord	Eccentrically placed
Any specific lesions	Basal yellow brown nodule, 1.0cm from cord insertion	None	None	Retroplacental haematoma with parenchymal indentation Subchorionic haematoma Intervillous thrombus	None
Microscopy	Intervillous thrombi	Distal villous immaturity	Vascular ectasia of chorionic plate, stem villous vessels and hypercapillarisation of distal villi	Retroplacental and subchorionic haematoma, intervillous thrombus, C/W abruption	Fibrin thrombi in the decidual Vessels and focal laminar necrosis
	Infarct	Patchy chorangiomas	Distal villous immaturity		Distal villous immaturity
	Laminar necrosis, decidua	Lowgrade, focal villitis of unknown aetiology			Maternal vascular underperfusion
	Maternal vascular underperfusion				

Table 3: Patients with idiopathic thrombocytopenic purpura and other diseases.

Details	Patient 8	Patient 9A	Patient 9B	Patient 10
Maternal age	26 years	29 years	31 years	27 years
autoimmune etiology	ITP	ITP	ITP	ANA positive
Duration since diagnosis	2 years	14 years	16 years	20 weeks of gestation
Laboratory data	Severe Thrombocytopenia	Severe Thrombocytopenia, ANA-Anticytoplasmic antibodies positive	Severe Thrombocytopenia, ANA-Anticytoplasmic antibodies positive	ANA-Anticytoplasmic antibodies positive
Previous obstetric history	G1-normal vaginal delivery G2-PP	Primi	G1- normal vaginal delivery, postpartum splenectomy G2-PP	Primi
Gestational age at delivery	38W+6D	36W+6D	38W+4D	37W+4D
Course during pregnancy/complications	-	PPROM, Oligohydramnio, Postpartum splenectomy	Oligohydramnios	Subclinical hypothyroidism
Treatment during pregnancy	Platelet transfusions	IV Ig, steroids, platelet transfusions	Steroids, platelet transfusions	LMWH from 20 weeks
Foetal outcome	AGA, live born	AGA, liveborn	AGA, liveborn	SGA, liveborn
Foetal weight	2.6kg	2.33kg	3.05 kg	2.23kg
Gross				
Placental weight	312.0gms (<10 th percentile)	358.0gms (<10 th percentile)	410.0gms (=10 th percentile)	386.0gms (<10 th percentile)
Cord	Eccentrically placed, edematous cord	Eccentrically placed, flat, hypocoiled cord	Hypercoiled, edematous cord	Hypocoiled cord
Any specific lesions	2 full thickness firm yellow lesions with central haemorrhagic area	Three basal wedge shaped, pale brown, firm areas	None	Three basal to full thickness, firm yellow brown lesions
Microscopy	Intervillous thrombi	Massive perivillous fibrin deposition(transmural)	Haemorrhage around the three umbilical vessels	Decidual laminar necrosis
	Infarcts	Intervillous thrombi	Decidual laminar necrosis	Infarcts
	DVH, hypercapillarization, increased syncytial knots, C/W maternal vascular underperfusion	Lymphocytic deciduitis	Incipient chorangiomas	Chorionic plate and stem villous vessels show fibrin thrombi
			Maternal vascular underperfusion	Large Foci of avascular hyalinized villi
				DVH, hypercapillarization, increased syncytial knots, C/W maternal vascular underperfusion and foetal vascular obstruction

DISCUSSION

Many physiological changes must occur to allow the fetus to persist and grow. Part of the implantation process involves syncytiotrophoblast invasion and erosion of maternal endometrial blood vessels resulting in the development of a utero-placental circulation. Ultimately, the trophoblast becomes incorporated into the

wall of the vessel which has now become a thin walled, dilated vascular channel with lack of muscle, thereby ensuring an adequate blood supply to the developing fetus. These vascular changes have been termed physiological change and lack of physiological change or decidual vasculopathy has been found to be a significant placental feature in certain diseases, for example preeclampsia alone, chronic hypertension with

superimposed preeclampsia, autoimmune diseases and idiopathic SGA infants.⁸⁻¹⁰

In this report, we describe clinical and pathologic findings of 11 placentas from 10 patients with autoimmune diseases. We prefer to specify the lesions that are present rather than to embrace them all in the imprecise terminology of placental insufficiency. The primary pathology observed in the present study was maternal vascular underperfusion (fibrin thrombi in the decidual vessels, intervillous thrombi, infarcts, distal villous hypoplasia and increased syncytial knotting).⁸⁻¹⁰ Interestingly, the other pathological features observed were chorangiomas, villitis, massive perivillous fibrin deposition, distal villous immaturity, abruption and foetal thrombotic vasculopathy.

Distal villous immaturity (DVI) is a maturation defect of the terminal villi.¹³ Microscopically the terminal villi are enlarged with excessive stroma, increased vascularity, with a continuous layer of syncytiotrophoblast, paucity of vasculosyncytial membranes and lack peripheral polarization of capillaries. This in turn decreases the efficiency of maternal-foetal exchange leading to late gestational hypoxia and IUFD. This finding is most often associated with maternal diabetes. DVI was apparent in the only term IUFD of our study. Contrary to the observations made so far in the literature, there was no evidence of glucose intolerance in the mother, but she had primary APLA. Presence of DVI in autoimmune diseases remains speculative and needs further characterization.

Chorangiomas involves immature intermediate villi or stem villi and the vessels are surrounded by pericytes with increased stromal cellularity and collagen. Diffuse multifocal chorangiomas is associated with extreme prematurity, IUGR, preeclampsia and it has been suggested that it may be a developmental abnormality of the villi.¹⁴ This was the major lesion along with maternal vascular underperfusion in one of the studied SLE patients with secondary APLA. The pregnancy was complicated by preeclampsia, prematurity and intrauterine growth restriction.

The other patient who had SLE with secondary APLA was diagnosed postpartum and was not treated antenatally. She had a severe growth retarded foetus which resulted in stillbirth. The predominant lesion in the placenta was villitis of unknown etiology (VUE), perivillitis and retroplacental haematoma.¹⁵ The villi were invaded and expanded by lymphohistiocytic infiltrate and showed secondary changes of ischemia, infarction, recanalizing thrombi in the stem villous vessels with resultant groups of avascular villi (foetal thrombotic vasculopathy).

VUE is a well-recognized entity, but remains a significant challenge because of its frequency, high recurrence rate and associated poor outcome. The most

accepted theory is that VUE is an immune reaction akin to placental "rejection".¹⁶

Thrombi in the foetal circulation of the placenta cause a pattern of clustered avascular fibrotic villi called foetal thrombotic vasculopathy (FTV). Causal factors of FTV include stasis, maternal autoimmune diseases and vascular injury. The most serious outcomes include growth restriction, neurologic injury and perinatal death.^{6,7}

Our patient with ANA positivity also had foetal thrombotic vasculopathy with superimposed maternal vascular under perfusion and resultant SGA baby.^{11,12}

Apart from maternal vascular underperfusion, one of the placenta of ITP patient also showed massive perivillous fibrin deposition/maternal floor infarction (MPVFD/MFI). This particular patient had active disease during pregnancy and was treated with immunoglobulins, steroids and had improved pregnancy outcome. MPVFD/MFI has a recurrence rate of 30% or more.¹⁷ We had an opportunity to study the subsequent pregnancy of the same patient where the lesion did not recur. There were no associations found between placental lesions and foetal outcome in all three studied ITP cases.

CONCLUSION

Placenta remains an undervalued and underutilized surgical specimen in the evaluation of maternal autoimmune disorders. Studies have clearly demonstrated that there are a multitude of mechanisms where by autoimmunity can prevent normal placental development and can cause significant pathology. In this group of diverse autoimmune diseases placental lesions were not specific for any of them.

But it appears that diseases that are clinically more severe have more severe placental vascular changes, related to foetal outcome.

Therefore, although the histopathologic lesions are similar, there appears to be a "grading" in severity. Placental thrombosis and infarction are just one part of the placental lesions. Analyzing previous placentas has been helpful as patients appear to repeat the recurrent lesions such as VUE, MPVFD/MFI and DVI. Pathologists should be aware of these changes and alert the clinicians to the possibility of recurrences in subsequent pregnancies.

Given the heterogeneity of histologic findings, it would be unlikely that a single treatment would be effective in all cases. Perhaps placental pathology should be used to guide therapy; however, it needs to be validated by a study on a larger sample. Placental examination should be indicated in defined subset of patients which includes maternal autoimmune disorders.

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