Scientific Research Publishing

Open Journal of Pathology, 2026, 16(2), 103-116
https://www.scirp.org/journal/ojpathology
ISSN Online: 2164-6783
ISSN Print: 2164-6775

Study of the Placenta in the Context of Fetal Pathology Related to COL4A1/A2

Amadou Ndiade[1,2*], Mame Venus Gueye[3], Ndiaga Diop[3]

[1]Histology, Embryology and Cytogenetics Laboratory, Alioune Diop University, Bambey, Senegal
[2]Fetopathology Department, Necker-Enfants Malades Hospital, Paris, France
[3]Histology, Embryology and Cytogenetics Laboratory, Cheikh Anta Diop University, Dakar, Senegal
Email: *amadou.ndiade@uadb.edu.sn

How to cite this paper: Ndiade, A., Gueye, M.V. and Diop, N. (2026) Study of the Placenta in the Context of Fetal Pathology Related to COL4A1/A2. *Open Journal of Pathology*, **16**, 103-116.
https://doi.org/10.4236/ojpathology.2026.162012

Received: January 8, 2026
Accepted: February 23, 2026
Published: February 26, 2026

Abstract

Introduction: Structural alterations of type IV collagen resulting from genetic mutations or immune-mediated injury disrupt epithelial integrity and lead to organ dysfunction. The α1 (IV) and α2 (IV) chains are key components of type IV collagen within the basement membrane of vascular endothelium. To date, few studies have specifically investigated placental lesions associated with COL4A1/A2-related fetal pathology, and only limited cases describing fetal vascular malperfusion have been reported. **Materials and Methods**: This study includes ten cases of COL4A1/A2-related fetal pathology collected following a collaborative call issued by the French Society of Fetopathology (SOFFOET). All placentas were re-examined histologically using hematoxylin-eosin-saffron (HES)-stained sections, including systematic evaluation of the umbilical cord, membranes, and a minimum of four placental parenchymal samples per case. Immunohistochemistry using anti-collagen IV antibodies and special histochemical stains (PAS, green trichrome, and orcein) were performed in five cases and in two control cases with hemorrhagic brain pathology without COL4A1/A2 abnormalities. **Results:** Ten fetuses were included in the study. Dysmorphic features were present in five cases, and congenital malformations in three. All cases showed cerebral ischemic and hemorrhagic lesions. One fetus carried a COL4A2 mutation with a normal COL4A1 gene, whereas the remaining fetuses had COL4A1 mutations. Eight placentas were normotrophic and two hypertrophic, with no hypotrophic placentas identified. Fetal vascular malperfusion lesions were observed in five cases. **Discussion:** All cases in this series were index cases with no known family history, except for a history of intracranial aneurysms in one case, in which the COL4A1 variant occurred de novo. Endothelial detachment of chorionic and stem villous vessels and vacuolization of the tunica media were observed both in the study cases and in the control, placentas lacking COL4A1/A2 variants, sug-

gesting these findings may be non-specific. Immunohistochemical staining for collagen IV did not reveal overt abnormalities of the endothelial basement membrane, possibly due to acute hypoxic injury related to medical termination of pregnancy.

Keywords

COL4A1/A2, Fetal Pathology, Placental Pathology

1. Introduction

Type IV collagen belongs to a family of collagen proteins comprising at least 25 distinct members. The COL4A1, COL4A2, COL4A3, COL4A4, COL4A5, and COL4A6 genes encode the six *α* chains of type IV collagen [1]. These chains (*α*1 [IV] to *α*6 [IV]) are selectively expressed in different basement membranes at various stages of embryonic development [2]. This selective expression underlies the tissue-specific distribution of disease and the resulting clinical manifestations. Structural alterations of type IV collagen, whether caused by genetic mutations or immune-mediated injury, disrupt basement membrane integrity and lead to organ dysfunction [3].

The *α*1 and *α*2 chains constitute the predominant form of type IV collagen in the basement membrane of the vascular endothelium [4]. Consequently, COL4A1/A2-related disorders encompass a broad spectrum of vascular abnormalities with multi-organ involvement, affecting the brain, kidney, eye, heart, bone marrow, and skeletal muscle [5].

Neurological involvement is a major feature of COL4A1/A2-related pathology and includes ischemic lesions such as porencephaly and schizencephaly, as well as intracranial hemorrhages [6]. In a series of 18 cases of fetal cerebral hemorrhages, 5 cases had a COL4A1 mutation [4], supporting a causal role for COL4A1/A2 variants in fetal brain injury. In contrast, placental findings in COL4A1/A2-related pathology have been only sparsely described, with few studies addressing fetal vascular lesions [6]. Some reported cases have shown features of fetal vascular malperfusion (FVM), suggesting a possible placental contribution to the pathogenesis of cerebral lesions.

Fetal vascular malperfusion was first described in 1995 by Redline and Pappin under the term fetal thrombotic vasculopathy [7] encompassing occlusive lesions of the fetal circulation involving the umbilical, chorionic plate, stem villous, and terminal villous vessels. Five main lesion types were defined: mural or occlusive thrombosis, avascular villi, intramural fibrinoid deposits or endothelial cushions, hemorrhagic endovascular inflammation, and fibromuscular sclerosis. The Amsterdam Placental Workshop Group consensus subsequently refined the classification of FVM, defining two major patterns segmental and global and two grades of severity (low-grade and high-grade) [8] Segmental FVM reflects thrombotic occlusion or obliteration of chorionic plate or stem villous vessels, resulting in

complete downstream villous obstruction. Global FVM corresponds to partial or intermittent obstruction of umbilical blood flow and is characterized by venous ectasia, intramural fibrin deposition in large vessels, and/or small foci of avascular or karyorrhectic villi distributed over a wide placental area. High-grade FVM is reserved for severe forms and is defined by the presence of multiple foci of avascular villi or a single focus of another qualifying lesion, including extensive thrombosis of chorionic plate or stem villous vessels [8].

In this context, the present study reports a retrospective series of ten fetal cases with COL4A1/A2-related pathology, with two main objectives: (i) to identify placental lesions potentially associated with ischemic and hemorrhagic cerebral lesions, and (ii) to evaluate the structural integrity of fetal placental vessels.

2. Patients and Methods

2.1. Study Design and Population

This study includes 10 fetal cases with COL4A1/A2-related pathology, collected following a collaborative call issued by the French Society of Fetopathology (SOFFOET). Fetuses were referred to prenatal diagnosis centers due to cerebral abnormalities detected on ultrasound. In all cases, the severity of the lesions led to termination of pregnancy (TOP).

2.2. Study Centers

Fetoplacental examinations were performed at the fetal pathology unit of Necker Hospital (n = 5) and five additional fetopathology units: Institut de Puériculture et de Périnatalogie (Paris), Rennes University Hospital, Lyon Hospitals (Groupe Hospitalier Nord), Toulouse University Hospital, and the Institute of Pathology and Genetics (Gosselies, Belgium).

2.3. Data Collection

For each case, the following data were collected:

- Clinical and antenatal findings (**Table 1**).
- Main autopsy findings, performed according to a standardized protocol in each centre (**Table 2**).
- Results of molecular genetic analyses (**Table 3**).
- Macroscopic placental findings (**Table 4**).

2.4. Placental Examination

All placentas were re-examined microscopically using haematoxylin-eosin-saffron (HES) staining, including systematic examination of the umbilical cord and membranes, with a minimum of four parenchymal samples per placenta.

2.5. Immunohistochemistry and Special Staining

Immunohistochemical staining with an anti-type IV collagen antibody and special stains (PAS, Masson's trichrome, orcein) were performed on five cases from the

series and on two control cases with haemorrhagic cerebral pathology without COL4A1/A2 abnormalities.

2.6. Control Cases

Control cases were selected based on the presence of haemorrhagic cerebral pathology and the absence of COL4A1/A2 mutations. They were not specifically matched for gestational age (GA) or mode of termination, but importantly, none of the control cases exhibited placental or neuropathological features suggestive of acute hypoxic-ischaemic injury. This selection strategy aimed to minimize potential confounding related to gestational age or procedure-related hypoxia when interpreting acute hypoxic lesions in the study group.

3. Results

3.1. Study Population

The study population consisted of 10 fetuses ten fetuses with COL4A1/A2-related pathology.

3.2. Clinical and Imaging Features

All fetuses were referred to prenatal diagnostic centers for fetal brain abnormalities detected on second-trimester ultrasound. In one family (case 1), a relevant family history was identified, with intracranial aneurysms reported in the mother and paternal aunt. Consanguinity was noted in one case (case 3). Detailed clinical and prenatal imaging findings are summarized in Table 1.

Table 1. Clinical and imaging features of the fetal cases.

Case	Family history	Gravidity/ Parity	Gestational age at diagnosis (weeks)	Prenatal imaging findings
Case 1	Intracranial aneurysms (mother and paternal aunt)	G1P0	Not specified	Unilateral cerebral atrophy
Case 2	None	G1P0	29	**US:** Bilateral temporal schizencephaly **MRI:** Bilateral perisylvian schizencephaly, cerebral atrophy, polymicrogyria
Case 3	Consanguinity (first cousins)	G2P1	25	**MRI:** Polymicrogyria, schizencephaly, ventriculomegaly, extensive venous thrombosis of the straight sinus
Case 4	None	G3P1	22	**US:** Clastic-appearing cerebral lesions, corpus callosum dysgenesis
Case 5	None	G3P1	28	**US:** Bilateral schizencephaly
Case 6	None	G2P1	23	**US:** Polymalformative syndrome: ventricular septal defect, ventriculomegaly, small cerebellum, right parietal schizencephaly, corpus callosum dysgenesis

Continued

Case 7	None	Not available	18	**US:** Partial agenesis of the corpus callosum (absence of rostrum and splenium), cerebellar hypoplasia, right renal agenesis, cardiac failure
Case 8	None	G3P1	27	**US:** Suspected left schizencephaly **MRI:** Complete parenchymal rupture of the left insular lobe with hemorrhagic margins, right frontal venous thrombosis
Case 9	None	G1P0		Hemorrhagic brain lesions
Case 10	None	G2P1		MRI: right intraventricular clot

3.3. Autopsy Data Including Neuropathology

Termination of pregnancy was performed during the second trimester in six cases and during the early third trimester in four cases. Dysmorphic features were observed in five fetuses, and extracerebral malformations were identified in three cases. Neuropathological examination revealed a wide spectrum of ischemic, destructive, and hemorrhagic cerebral lesions (Table 2).

Table 2. Clinical characteristics and neuropathological findings.

Case	Gestational age at termination (weeks)	Sex	External and internal abnormalities	Neuropathological findings
Case 1	23	Male	No associated extracerebral abnormalities	Cerebral hemiatrophy with cavitary necrosis involving the right middle cerebral artery territory
Case 2	33	Female	No associated extracerebral abnormalities	Bilateral perisylvian porencephaly and occipital schizencephaly associated with severe cerebral atrophy
Case 3	27	Female	No associated extracerebral abnormalities	Foci of ruptured subependymal haemorrhage; diffuse post-haemorrhagic remodelling; cortical ribbon necrosis; destruction of the prehippocampal cortex; capillary proliferation of the periventricular white matter; petechial haemorrhages; calcified necrosis; small foci of polymicrogyria; asymmetry of the anterior limbs of the internal capsule. Brainstem involvement included coagulum in resorption within the posterior fossa, cerebellar and tectal necrosis, and reduction of projection pathways
Case 4	23	Female	No associated extracerebral abnormalities	Left fronto-parietal cortical necrosis associated with schizencephaly
Case 5	29	Female	Marked saddle nose; bilateral camptodactyly; duplicated ureter and duplicated renal pelvis on the right	Left fronto-parietal cortical necrosis associated with schizencephaly

Continued

Case 6	26	Male	Macrocephaly; ovoid facial appearance; accentuated infraorbital sulcus; broad nose with low nasal tip; protruding tongue; right ear with low-set attachment, hypoplastic helix, and poorly defined contour. Ventricular septal defect (VSD) diagnosed at admission	Microcephaly with left porencephalic lesion; multiple foci of polymicrogyria; ventricular dilatation; diffuse deep necrotic-haemorrhagic lesions; conjunctivo-vascular hamartomatous lesion of the left cerebellar tentorium
Case 7	27	Female	Craniofacial dysmorphia; unicornuate uterus; agenesis of the right uterine adnexa; intestinal malrotation; right renal agenesis; single umbilical artery (SUA); left ventricular wall thickening	Foci of cerebral microhaemorrhage with glomeruloid-like vascular proliferation and tortuous arterial architecture
Case 8	29	Male	No associated extracerebral abnormalities	Ischaemic-haemorrhagic remodelling of the left Sylvian fissure with schizencephaly; peripheral polymicrogyria; multiple areas of gliosis; haemorrhagic suffusions with siderophages. Parenchymal haemorrhage in the right frontal horn with peripheral gliotic remodelling. Bilateral porencephalic cavities. Small area of old ischaemic-haemorrhagic remodelling in the right temporal lobe
Case 9	25	Male	Craniofacial dysmorphia	Left porencephaly with post-haemorrhagic lesions
Case 10	32	Male	Mild hypertelorism	Cerebral atrophy (biometry <5th percentile); severe bilateral cortical and subcortical lesions; cavitary perisylvian lesions associated with a non-communicating occipital cleft-type lesion

Overall, all fetuses exhibited cerebral hemorrhagic and/or ischemic lesions. The distribution of the main neuropathological lesions is summarized in Table 3.

All foetuses had cerebral, clastic and hemorrhagic lesions.

Table 3. Distribution of cerebral lesions.

Neuropathological lesion	Number of cases (n)	Frequency (%)
Porencephaly	2	20
Schizencephaly	3	30
Cerebral atrophy	2	20

Continued

Cortical necrosis	5	50
Hemorrhagic foci	6	60

3.4. Genetics Findings

Genetic analysis identified a COL4A2 mutation in one case (case 1), which was the only case with a normal COL4A1 gene. All remaining cases harbored pathogenic variants in COL4A1. Detailed molecular genetic results are presented in Table 4.

Table 4. Molecular genetic analysis.

Case	Gene (RefSeq)	cDNA change (HGVS)	Exon	Protein change	Mode of transmission
Case 1	COL4A1/A2 (NM_001845.4)	c.2980G > A	NA	p.(Gly994Arg)	De novo
Case 2	COL4A1/A2 (NM_001845.4)	c.4738G > A	NA	p.(Gly1580Ser)	Maternal
Case 3	COL4A1/A2 (NM_001845.4)	c.3139G > A	37	p.(Gly1047Arg)	De novo
Case 4	COL4A1/A2 (NM_001845.4)	c.4566G > C	49	p.(Trp1522Cys)	De novo
Case 5	COL4A1/A2 (NM_001845.4)	c.2485G > T	32	p.(Gly829Cys)	De novo
Case 6	COL4A1/A2 (NM_001845.4)	c.4843G > A	NA	p.(Glu1615Lys)	De novo
Case 7	COL4A1/A2 (NM_001845.4)	c.3131G>A	NA	p.(Gly1044Asp)	De novo
Case 8	COL4A1/A2 (NM_001845.4)	c.3715G > A	42	p.(Gly1239Arg)	De novo
Case 9	COL4A1/A2 (NM_001845.4)	c.4040G > T	46	p.(Gly1347Val)	De novo
Case 10	COL4A1/A2 (NM_001845.4)	c.144 + 5G > A	NA	p.?	De novo

3.5. Placental Examination

3.5.1. Macroscopic Findings

Umbilical cord abnormalities were observed in three cases, including marginal insertion (cases 4 and 6) and excessive coiling with deep grooves (case 5). Eight placentas were normotrophic, while two were hypertrophic; none were hypotrophic. The placento-fetal index was within normal limits in eight cases and increased in two cases (cases 6 and 7). Macroscopic placental findings are detailed in Table 5. Eight fetuses had placento-fetal indices within normal limits, whereas two cases showed elevated indices (cases 6 and 7).

Table 5. Macroscopic data for the placenta.

Case	GA	Cord abnormalities	Placenta	Standards	P/F index	Percentile norms
Case 1	23	None	165 g	25^e - 50^e	24.6% Normal	10^e - 25^e
Case 2	33	None	332g	25^e - 50^e	17.8 Normal	50^e - 75^e
Case 3	27	None	302g	50^e - 75^e	30.1% Normal	50^e - 75^e
Case 4	23	Marginal	139	10^e - 25^e	26.6% Normal	10^e - 25^e
Case 5	29	Excessively coiled	250	25^e - 50^e	23.6% Normal	75^e - 90^e
Case 6	26	Marginal	321	90^e - 95^e	37.5 High	90^e - 95^e
Case 7	27	Edematous	349	90^e - 95^e	35.75 High	90^e - 95^e
Case 8	29	None	224	25^e - 50^e	18 Normal	25^e - 50^e
Case 9	25	None	170	25^e - 50^e	20 Normal	10^e - 25^e
Case 10	32	None	375	50^e - 75^e	Not defined	Not defined

3.5.2. Microscopic Findings

No specific microscopic lesions were identified in five cases. In the remaining five cases, no inflammatory lesions or erythroblastosis were observed. Discrete lesions of maternal vascular malperfusion, consisting of focal distal villous hypoplasia, were identified in three cases (cases 1, 3, and 8).

Lesions consistent with fetal vascular malperfusion were observed in five cases. These included fibromuscular sclerosis (five cases), intramural fibrin deposition or endothelial cushions (cases 2 and 5), and non-occlusive thrombosis (case 5). No classical foci of avascular villi, as described by Redline, were identified; however, large villous trunks or broad villi occasionally appeared sclerotic and avascular. Microscopic placental findings are summarized in Table 6.

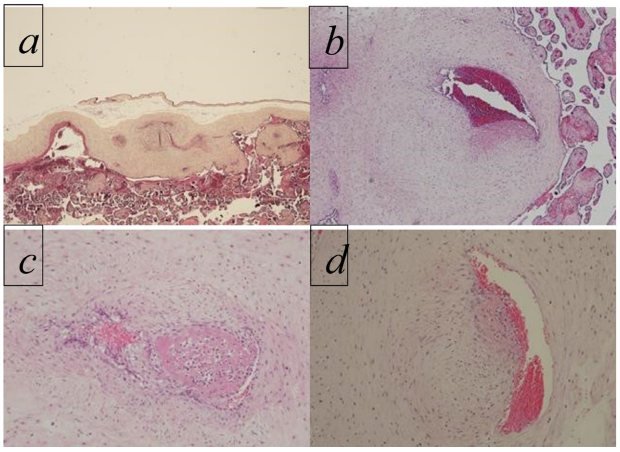
Table 6. Microscopic data from the placenta.

Case	SA	MVF patterns and grades	MVF lesions	Other lesions
Case 1	23	-	Absence	Advance villous maturation
Case 2	33	Overall MVF low grade	Fibromuscular sclerosis Endothelial cushion	Tortuous vessels and thickened wall
Case 3	27	-	Absence	Large villi (placenta of fetal anemia) advanced villous maturation
Case 4	23	Overall	Fibromuscular sclerosis	-
Case 5	29	Overall low grade	Wall thrombosis Endothelial cushion Fibromuscular sclerosis	Chorangioma homogeneous lesions
Case 6	26	Overall low grade	Fibromuscular sclerosis	-

Continued

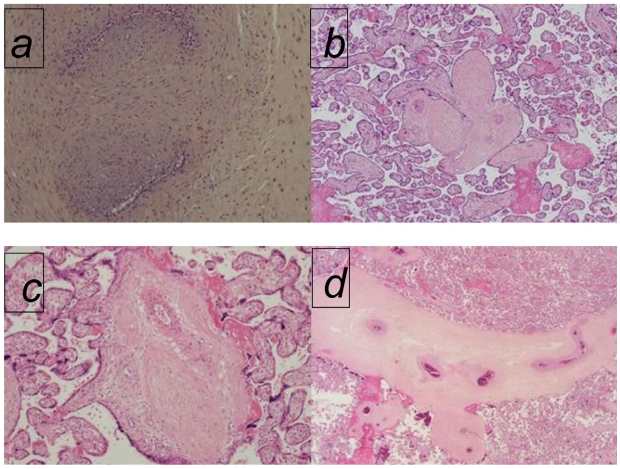
Case 7	27	-	Absence	-
Case 8	29	-	Absence	Advanced villous maturation
Case 9	25	-	Absence	-
Case 10	32	Segmentary low grade	Fibromuscular sclerosis	-

Representative histological features of placental vascular lesions, identified using standard staining, are illustrated in Figure 1 and Figure 2.



a. case 4 magnification X2 HES vessels under the chorionic plate showing fibro-muscular sclerosis. b. case 5: magnification 4× HES, intramural fibrin deposit known as endothelial cushion. c. case 5 ×10, HES obstructive thrombosis. d. case 5 magnification 10 HES endothelial cushion.

Figure 1. Histological appearance of the placenta with standard staining.

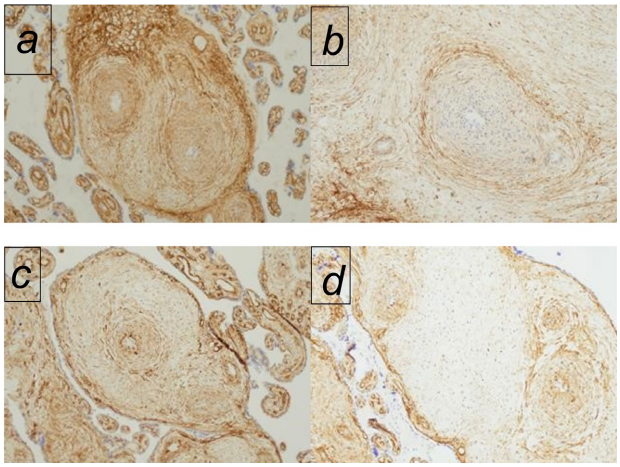


a. case 6: magnification 10 HES fibromuscular sclerosis. b. case 10 magnification 1 HES fibromuscular sclerosis. c. case 10 magnification ×4 fibromuscular sclerosis. d. case 1 magnification ×10 HES fibromuscular sclerosis.

Figure 2. Histological appearance of placental lesions with standard staining.

3.5.3. Structure of Chorionic and Stem Villous Vessels

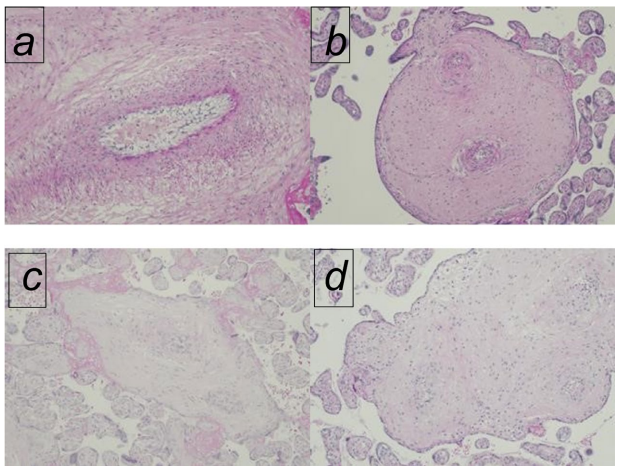
Immunohistochemical analysis using anti-type IV collagen antibodies demonstrated positive labeling in control cases and in the study cases, with labeling restricted to small villi and absent in large villous trunks. Marked peripheral vascular labeling was also observed (Figure 3).



a. control case with cerebral hemorrhages, positive staining. b. control case with placental malperfusion lesion, negative staining. c. case 2, positive staining of small villi and negative staining of large trunks. d. case 5, negative staining.

Figure 3. Anti-col-IV immunostaining magnification ×10.

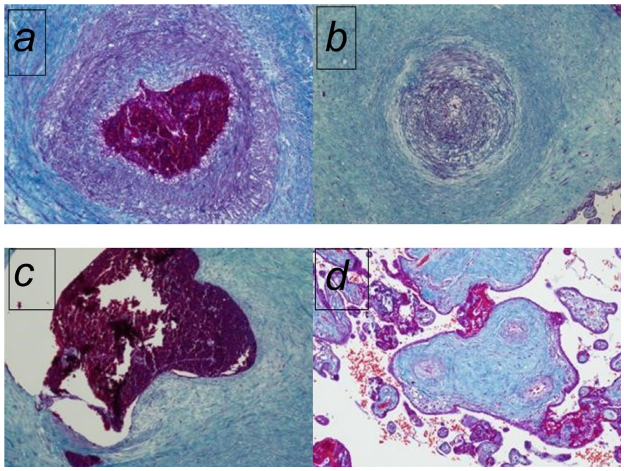
Periodic acid-Schiff (PAS) staining revealed numerous vacuoles within the arterial media, with weak or absent staining in the study cases compared with strong positive staining in control cases (Figure 4). Masson's trichrome staining demonstrated a marked reduction or complete loss of smooth muscle fibers within



a. control case with cerebral hemorrhages PAS positive presence of media vacuoles. b. control case with placental malperfusion lesion PAS positive presence of media vacuoles. c. case 2 PAS negatives with presence of media vacuoles. d. case 4 PAS negative with presence of media vacuoles.

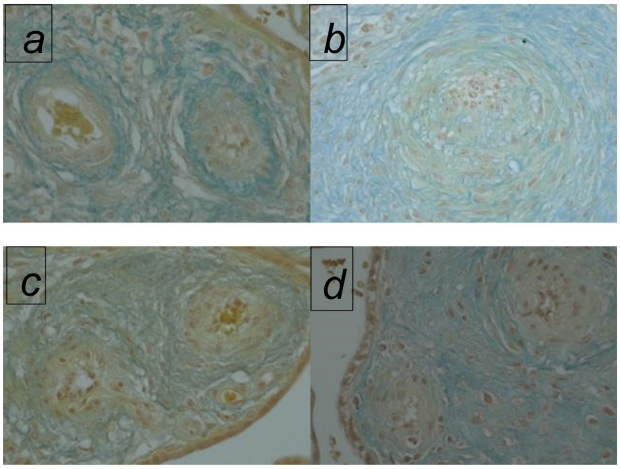
Figure 4. Histological appearance of the placenta at 10× magnification, PAS staining.

the arterial media in all study cases, whereas control cases showed a normal distribution of muscle fibers (Figure 5). Orcein staining revealed a significant reduction or absence of elastic fibers in arterial walls in the study cases, while elastic fibers were preserved and clearly identifiable in control cases (Figure 6).



a. control case with cerebral hemorrhages, good distribution of muscle fibers in the arterial media. b. control case with placental malperfusion lesion, well-organized muscle fibers. c. case 2 endomural fibrin deposit, known as endothelial cushion appearance. d. case 1 effacement of muscle fibers in the arterial media.

Figure 5. Histological appearance of the placenta at 10× magnification, stained with Masson's trichrome stain.



a. control case with cerebral hemorrhages presence of elastic fibers in the arterial wall. b. control case with placental malperfusion lesions, presence of elastic fibers in the arterial wall. c. Case 2: absence of elastic fibers inside the arterial wall. d. Case 5: absence of elastic fibers inside the arterial wall.

Figure 6. Histological appearance of the placenta at 40× magnification, orcein staining.

4. Discussion

We report ten cases of fetal pathology associated with COL4A1/A2 mutations, reflecting the rarity of this condition in the antenatal period. Previous reports in-

clude eight cases compiled by Gubana *et al*. [9] and four cases reported in Washington [6]. In families undergoing systematic screening, the number of identified cases increases; for example, Meuwissen *et al*. [10] described 183 cases in 13 families.

Our series includes only index cases with no known family history, except for one case (Case 1) with a history of intracranial aneurysms; in this fetus, the COL4A1 variant appeared de novo. Molecular genetic analysis identified ten variants (**Table 4**), nine of which were de novo and one maternally inherited. De novo transmission predominates in several studies [9] and limits recurrence risk, although residual risk may exist due to mosaicism.

Neuropathological findings were detected after 22 weeks of gestation. Six cases exhibited hemorrhagic and ischemic lesions (schizencephaly and porencephaly), whereas four cases presented only ischemic lesions. In previously reported familial cases [10], two patients showed focal cortical malformations: one with a maternally inherited COL4A1 mutation had schizencephaly, porencephaly, and intraventricular hemorrhage, while a second with a paternal COL4A2 mutation displayed left frontal porencephaly and cortical dysplasia.

Mouse models of COL4A1-related pathology demonstrate porencephaly secondary to focal ruptures of the vascular basement membrane [11]. Approximately 50% of mutant mice die from cerebral hemorrhage within the first day of life, and 18% of survivors develop porencephaly, highlighting the pathogenic role of vascular fragility.

Placental and fetal vascular findings have rarely been described in COL4A1/A2 pathology [6] [9]. In our series, five cases exhibited no fetal vascular malperfusion (FVM) lesions or other placental abnormalities, consistent with previous reports: one case in Shannon's series and four in Gubana's series also showed no FVM lesions [6] [9].

In all ten cases, as well as in the two control cases without COL4A1/A2 variants, we observed endothelial detachment in chorionic and stem villous vessels, together with tunica media vacuolization. This medial vacuolization has been described previously by Shannon *et al*. [6]; however, we consider it non-specific, as it is commonly observed post-mortem in placentas from deceased fetuses, irrespective of etiology. In contrast, the fetal vascular malperfusion lesions observed in the five remaining cases were predominantly fibromuscular sclerosis of chorionic and stem villous vessels. The absence of similar lesions in controls argues against procedure-related or post-mortem artefacts and supports their intrinsic association with COL4A1/A2-related pathology.

No old, intramural, or occlusive thromboses were observed, except for one recent thrombosis in Case 5, associated with extensive vascular lesions (intramural fibrin deposits, fibromuscular sclerosis, and chorangioma) and obstructive funicular pathology (hyper-spiral cord). These lesions cannot be definitively attributed to the COL4A1/A2 variant.

Foci of avascular villi, classically evaluated semi-quantitatively according to the

Amsterdam criteria [8], were absent. Instead, large fibrohyaline villous trunks without residual vascular structures were observed. Intramural fibrinoid deposits or endothelial cushions were present in Case 2 (without funicular pathology) and Case 5 (with obstructive funicular pathology). These lesions represent focal vascular injury or old thrombosis [12].

The fibromuscular sclerosis affecting chorionic and trunk vessels in five cases was not associated with placental insufficiency: placentas were normotrophic, without infarction or basal decidual hematoma, and maternal vascular malperfusion lesions were absent on microscopy. The sclerosis, which extended across multiple histological sections, often obliterated the vascular lumen and caused severe wall remodeling (**Figures 2(a)-(d)**). Its grading is not clearly defined in the Amsterdam classification [8].

Histochemical stains and anti-collagen IV immunostaining confirmed the loss of elastic fibers and disorganization of smooth muscle, particularly in the five cases with fibromuscular lesions, rendering it difficult to distinguish veins from trunk arteries (**Figure 1(c)**, **Figure 1(d)**, **Figure 6(c)**, **Figure 6(d)**). In control cases, arterial and venous walls were well preserved (**Figure 5(a)**, **Figure 5(b)**). These lesions may reduce vascular tone and lead to hypoperfusion, contributing to the cerebral hemorrhages observed in COL4A1/A2-related pathology.

5. Conclusion

COL4A1/A2-related fetal pathology is rare. Ischemic and hemorrhagic brain lesions are the main indicators prompting genetic investigation. The relationship between placental lesions, particularly fetal vascular malperfusion, and cerebral pathology remains incompletely understood. In our series of ten cases, fetal vascular malperfusion lesions were observed in half of the placentas. These lesions exhibited vascular sclerosis, occasionally obliterative, with hypertrophic walls lacking smooth muscle and elastic fibers. Such structural vascular alterations may be specifically associated with COL4A1/A2 variants.

Conflicts of Interest

The authors declare that there are no commercial or financial relationships that could be construed as a potential conflict of interest in relation to this study.

References

[1] Raija, S., Haka-Risku, T., Prockop, D.J. and Tryggvason, K. (1987) Complete Primary Structure of the *α*1-Chain of Human Basement Membrane (Type IV) Collagen. *FEBS Letters*, **225**, 188-194. https://doi.org/10.1016/0014-5793(87)81155-9

[2] Hudson, B.G., Reeders, S.T. and Tryggvason, K. (1993) Type IV Collagen: Structure, Gene Organization, and Role in Human Diseases. Molecular Basis of Goodpasture and Alport Syndromes and Diffuse Leiomyomatosis. *Journal of Biological Chemistry*, **268**, 26033-26036. https://doi.org/10.1016/s0021-9258(19)74270-7

[3] Hudson, B.G., Tryggvason, K., Sundaramoorthy, M. and Neilson, E.G. (2003) Alport's Syndrome, Goodpasture's Syndrome, and Type IV Collagen. *New England*

Journal of Medicine, **348**, 2543-2556. https://doi.org/10.1056/nejmra022296

[4] Plaisier, E. and Ronco, P. (2009) COL4A1-Related Disorders. GeneReviews®. University of Washington, Seattle; 2009-2020. https://www.ncbi.nlm.nih.gov/books/NBK7046/

[5] Bilguvar, K., DiLuna, M.L., Bizzarro, M.J., Bayri, Y., Schneider, K.C., Lifton, R.P., *et al*. (2009) COL4A1 Mutation in Preterm Intraventricular Hemorrhage. *The Journal of Pediatrics*, **155**, 743-745. https://doi.org/10.1016/j.jpeds.2009.04.014

[6] Shannon, P., Hum, C., Parks, T., Schauer, G., Chitayat, D., Chong, K., *et al*. (2021) Brain and Placental Pathology in Fetal COL4A1 Related Disease. *Pediatric and Developmental Pathology*, **24**, 175-186. https://doi.org/10.1177/1093526620984083

[7] Redline, R.W. and Pappin, A. (1995) Fetal Thrombotic Vasculopathy: The Clinical Significance of Extensive Avascular Villi. *Human Pathology*, **26**, 80-85. https://doi.org/10.1016/0046-8177(95)90118-3

[8] Khong, T.Y., Mooney, E.E., Ariel, I., Balmus, N.C.M., Boyd, T.K., Brundler, M., *et al*. (2016) Sampling and Definitions of Placental Lesions: Amsterdam Placental Workshop Group Consensus Statement. *Archives of Pathology & Laboratory Medicine*, **140**, 698-713. https://doi.org/10.5858/arpa.2015-0225-cc

[9] Gubana, F., Christov, C., Coste, T., Tournier-Lasserve, E., Benachi, A., Fallet-Bianco, C., *et al*. (2022) Prenatal Diagnosis of COL4A1 Mutations in Eight Cases: Further Delineation of the Neurohistopathological Phenotype. *Pediatric and Developmental Pathology*, **25**, 435-446. https://doi.org/10.1177/10935266221080134

[10] Meuwissen, M.E.C., Halley, D.J.J., Smit, L.S., Lequin, M.H., Cobben, J.M., de Coo, R., *et al*. (2015) The Expanding Phenotype of COL4A1 and COL4A2 Mutations: Clinical Data on 13 Newly Identified Families and a Review of the Literature. *Genetics in Medicine*, **17**, 843-853. https://doi.org/10.1038/gim.2014.210

[11] Gould, D.B., Phalan, F.C., Breedveld, G.J., van Mil, S.E., Smith, R.S., Schimenti, J.C., *et al*. (2005) Mutations in COL4A1 Cause Perinatal Cerebral Hemorrhage and Porencephaly. *Science*, **308**, 1167-1171. https://doi.org/10.1126/science.1109418

[12] Allias, F. (2010) Pathologie du placenta. Cas n° 4. Vasculopathie thrombotique fœtale. *Annales de Pathologie*, **30**, 290-295. https://doi.org/10.1016/j.annpat.2010.05.005

List of Abbreviations

Col IV	Collagen IV
Col4 A1	Collagen alpha one
Col4 A2	Collagen alpha two
FVV	Fetal vascular malperfusion
GA	Gestational age
HES	Hematoxylin-eosin-saffron staining
MRI	Magnetic resonance imaging (MRI)
PAS	Periodic acid shiff
SUA	**Single umbilical artery**
TOP	Termination of pregnancy
US	Ultrasound
VSD	Ventricular septal defect