Case
Report

Case Report of Alagille Syndrome in a Pregnant Patient: A Arrative Review of the Diagnosis and Treatment

Alejandro ROJAS-URREA[1], Daniela ARIAS-MARIÑO[2], Fernanda E. LANDINES-PEÑA[3], Brumel Armando NIÑO-PATARROYO[4], Lorena GARCÍA-AGUDELO[1]

Yopal, Casanare, Colombia

ABSTRACT

Alagille syndrome is a genetic disorder with an autosomal dominant hereditary pattern. Clinical manifestations include craniofacial, ocular, cardiac, hepatic, renal, vascular, and skeletal abnormalities with varying phenotypic penetrance; therefore, treatment would be targeted to the affected organs. A successful pregnancy in this pathology is uncommon and depends on the maternal features, particularly those that involve the cardiovascular and hepatobiliary systems. The objective of the manuscript is to present the case of a 24-year-old pregnant woman with a diagnosis of Alagille syndrome, her therapeutic challenge, and associated conditions.

Keywords: Alagille syndrome; Diagnosis; Pregnancy; Therapeutics

Gynecol Obstet Reprod Med 2025;31(3):221-225

Introduction

Alagille syndrome (ALGS), also known as Alagille-Watson syndrome or arteriohepatic dysplasia, is a genetic disorder with an autosomal dominant hereditary pattern (1). It is caused by pathogenic variants in NOTCH2 or JAG1 (2,3). The prevalence of ALGS may vary from 1:30,000 to 100,000 inhabitants (2). Clinical manifestations are wide-ranging, considering the involvement of fundamental components of the Notch signalling pathway, allowing a broad range of clinical manifestations, including craniofacial, ocular, cardiac, hepatic, renal, vascular, and skeletal abnormalities, with varying phenotypic penetrance. Normally, it is necessary to have three out of seven major clinical abnormalities to make a clinical diagnosis, which include cardiac defects, hepatic abnormalities, renal manifestations, skeletal defects, ophthalmologic abnormalities, dysmorphic facies, and vasculature manifestations (1-3). Management depends on the clinical findings. There are no specific strategies for managing ALGS. For example, liver disease, one of the most common manifestations, has guidelines in the neonatal population that include nutritional supplementation because it plays a crucial role in improving the prognosis and treating the associated malnutrition, as well as pharmacological treatment for cholestasis; however, in adults, in the absence of specific guidelines, the management is guided in the same way as in infants, and in cases of advanced liver disease, liver transplantation (LT) is an alternative (4,5). In addition, other clinical defects must undergo a specific treatment. The availability of surgical procedures for intra-abdominal vasculopathy, the corrective procedures in cases of structural renal anomalies, and corrective cardiac surgery for cardiac manifestations can be excellent examples of standard management considering the clinical spectrum and related conditions (4,6). The objective of the manuscript is to present the case of a 24-year-old pregnant woman with ALGS, considering the challenge this poses for obstetrician-gynaecologists, given that it can mimic several pathologies of interest in pregnancy, and expertise in this area is limited, due to the few cases of pregnancy in patients with ALGS who reach adulthood, and its treatment according to the affected organs.

[1] *Master of Public Health Health Research Department Hospital Regional de la Orinoquía, Yopal, Casanare, Colombia*
[2] *SP. in Bioethics, Health Research Department Hospital Regional de la Orinoquía, Yopal, Casanare, Colombia*
[3] *Health Research Department Hospital Regional de la Orinoquia, Yopal, Casanare, Colombia*
[4] *SP. in Pediatrics. Health Research Department, Hospital Regional de la Orinoquía.Yopal, Casanare, Colombia*

Address of Correspondence: *Alejandro Rojas-Urrea Master of Public Health, Health Research Department, Hospital Regional de la Orinoquía, Casanare, Colombia. Address 15th Street, 07-95. Marginal de la Selva. PC: 850001 Yopal, Casanare, Colombia arojasurrea.22@gmail.com*

Submitted for Publication: 26.05.2025 Revised for Publication: 08.08.2025 Accepted for Publication: 09.10.2025 Online Published: 28.10.2025

ORCID IDs of the authors: *ARU: 0009-0005-5990-106X* *DAM: 0000-0002-6615-1413* *FELP: 0009-0001-4542-5470* *BANP: 0009-0006-4044-162X* *LGA: 0000-0001-9557-0900*

QR Code	Access this article online
	www.gorm.com.tr • https://mndijital.medicalnetwork.com.tr gorm@medicalnetwork.com.tr
	DOI:10.21613/GORM.2025.1610

How to cite this article: *Rojas-Urrea A. Arias-Mariño D. Landines-Peña FE. Niño-Patarroyo BA. García-Agudelo L. Case Report of Alagille Syndrome in a Pregnant Patient: a Narrative Review of the Diagnosis and Treatment. Gynecol Obstet Reprod Med. 2025;31(3):221-225*

Case report

A 24-year-old woman with an ALGS medical history consulted the emergency room for epigastric pain and nausea. Four days before, she had taken a homemade pregnancy test, which was positive. On physician examination, her vital signs were normal. She had a holosystolic murmur grade IV, nail clubbing, pain in the upper part of the abdomen and distension, and an abdominal and lower limb skin rash.

Initial labs reported elevated transaminase levels and alkaline phosphatase and slight anaemia (Table I). An electrocardiogram showed a first-degree atrioventricular block, and an obstetric transabdominal ultrasound reported foetal biometry consistent with 17 weeks and 2 days. For this reason, additional studies were performed. A transthoracic ultrasound scan reported velocities and gradients over the pulmonary valve, suggesting pulmonary valve stenosis with low probability for pulmonary hypertension, and the rest of the findings were within the normal parameters. The patient was treated with ursodeoxycholic acid (600 mg every 12 hours) and continued management from a maternal-foetal medicine specialist.

Five months later, at 37 weeks and 1 day of pregnancy, she consulted the emergency room for uterine contractions, cervix dilatation, and rupture of the membranes with meconium in the amniotic fluid. On physical examination, her vital signs were normal. An ultrasound confirmed that the foetus was in a podalic position, and her cervix was found to be six centimetres dilated with 90% effacement. Due to the high obstetric risk, an emergency caesarean was performed without complications. Post-surgical laboratories reported elevated bilirubin levels, transaminase levels, and alkaline phosphatase (Table I).

In addition, a normal hepatobiliary ultrasound was performed; due to this, general surgery decided to amplify studies with magnetic resonance cholangiopancreatography, which showed a vesicular polyp, pancreatic ductal dilatation, hepatomegaly with signs of chronic liver disease, heterogeneous, nonspecific splenomegaly, bilateral diffuse nephropathy, bilateral pyelocaliceal ectasia (Figure 1), and butterfly dorsal vertebrae (Figure 2).

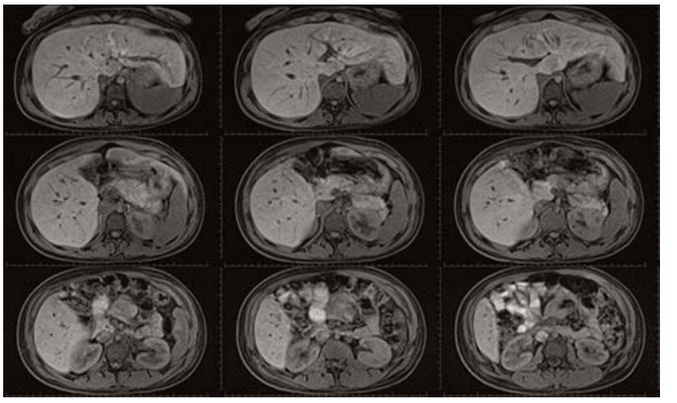

Figure 1: *Magnetic resonance imaging in sagittal slices shows a hepatomegaly of 180 mm with a liver with a heterogeneous parenchyma, a splenomegaly of 130 mm with a heterogeneous signal at the splenic parenchyma, and diffuse alteration in the corticomedullary renal signal, without evidence of lesions compatible with bilateral diffuse nephropathy.*

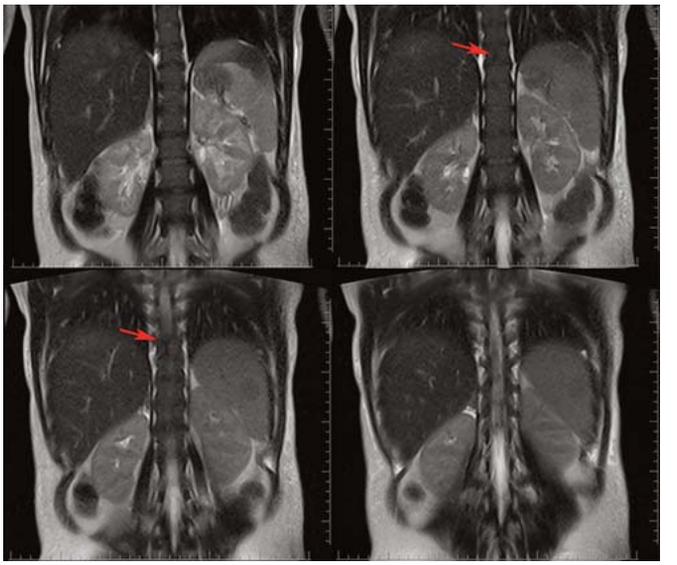

Figure 2: *Magnetic resonance imaging in coronal slices showing a dorsal vertebra (T8) with a partially visualised butterfly form (red arrows).*

Table I: *Laboratory record*

Laboratory	Reference range: nonpregnant adult	Second trimester of pregnancy	Post-caesarean section	Two days post-caesarean section
White blood cells	4-10 x 10^3/mm^3	10.49	5.13	9.47
Hemoglobin	12-16 g/dL	11.8	12	8.7
Hematocrit	35-44%	35.4	35.3	26
Platelets	150-400 x 10^3/mm^3	341	235	260
Total bilirubin	0.1 to 1.2 mg/dL	0.93	5.77	4.44
Indirect bilirubin	0.2-0.8 mg/dL	0.4	1.75	1.33
Direct bilirubin	< 0.3 mg/dL	0.53	4.02	3.11
Aspartate aminotransferase (AST)	5-40 U/L	77	84	47
Alanine aminotransferase (ALT)	7-56 U/L	124	116	67
Lipase	0-160 U/L	43.41		
Amylase	23-85 U/L	64.38	56.64	43.37
Phosphatase alkaline	44-147 U/L	555.33	438	304.3

The patient continued hospital management, improving liver function (Table I). Three days following the caesarean section, she displayed signs of induration and redness in the surgical wound. The soft tissue ultrasound revealed a collection of 17 × 19 mm in the scar, necessitating surgical drainage, which was completed without complications. The patient maintained a satisfactory clinical and paraclinical progression, underwent home management, and requested a genetic evaluation for her child.

Discussion

Diagnosing ALGS is difficult given the wide range of symptoms. Organ involvement may vary among family members carrying the same mutation (7). Clinical diagnosis requires the presence of at least three of the seven major clinical findings. Among cardiac abnormalities, peripheral pulmonary stenosis is the most common, followed by Tetralogy of Fallot (TOF). Other manifestations include atrial septal defects, ventricular septal defects, and aortic stenosis. In the ALGS, the right side of the heart is the preferred side to develop cardiac abnormalities (7, 8). Individuals with ALGS who exhibit cardiac manifestations experience poor outcomes with high morbidity and mortality rates (7).

The liver is the primary organ affected by ALGS, which includes symptoms and signs such as cholestasis, hyperbilirubinemia, xanthomas, pruritus, and cirrhosis (1,3). Approximately 20-30% of patients with liver compromise in ALGS require an LT; the main cause of the LT is portal hypertension and severe cholestasis with life-threatening complications (7). Facial abnormalities in ALGS patients vary due to the level of genetic penetrance. They are subtle in most cases but present in most patients. Classical manifestations include a prominent forehead, deep-set eyes, and a straight nose, which together create the shape of an inverted triangular face (2,7). Ocular features are mostly caused by the posterior embryotoxon, an asymptomatic condition without any visual consequence, and the presence of this entity is useful for the ALGS diagnosis. The optic disc drusen is another ocular defect described in ALGS, but its prevalence is low (1,2,7).

The other three organs involved are the skeleton, kidneys, and vascular systems (1-4). Regarding the first organ, approximately 44% of patients may exhibit butterfly vertebrae, primarily at the thoracic level; additional manifestations may include radio-ulnar synostosis and rib abnormalities (4). Kidney manifestations could occur in 30% of the patients, which include cysts, hypoplasia, hyper echogenicity, and functional issues like renal tubular acidosis (8). Vascular features hold significant importance, as they are the primary cause of non-cardiac deaths. Pulmonary arteries are the main arteries affected; others include intracranial, aortic, renal, and coeliac arteries (4,8).

Only a few ALGS cases with pregnancy have been documented in the literature (9,10). In 2022, Morton and Kumar reported two women with ALGS, and considering the rarity of this dual condition, the pregnancy outcomes have not been fully established in patients with ALGS (10). Pregnancy viability depends on maternal features, particularly those that are compromised in the cardiovascular and hepatobiliary systems, which may be exacerbated by the physiological alterations that occur during pregnancy, such as the progestogenic biliary stasis. As a result, some publications recommend using ursodeoxycholic acid during gestation in cases of elevated biliary acids to minimise the risk to the foetus, which includes distress with meconium-stained liquor, preterm delivery, and foetal death near the end of gestation (4).

Due to phenotypic variability, ALGS treatment would be directed to the affected organs and symptoms. It is recommended to perform complementary tests, such as echocardiograms, abdominal ultrasounds, chest X-rays, eye screenings, and magnetic resonance imaging, to diagnose abnormalities once the diagnosis is made or in cases of a highly suspicious one (11). Treatment for cholestasis in children and adults includes the use of ursodeoxycholic acid, rifampicin, antihistamines, and, in selected cases, naltrexone (4,12,13). An individual nutritional plan, which normally requires oral supplementation to achieve 130–150% of the normal requirement for the age, is recommended to avoid and treat malnutrition (7,14). For pruritus, treatment with ileal bile acid transporter (IBAT) inhibitors can be beneficial by interfering with the enterohepatic circulation of bile acids (4,5). Other therapies, such as dupilumab, can be an acceptable option in cases of refractory pruritus (14).

Surgery is the second line of treatment for liver disease. Partial external biliary diversion (PEBD) can reduce the amount of bile acids in the blood and produce a moderate control of xanthomas and pruritus. However, performing PEBD in some cases is not enough to prevent the realisation of an LT, especially in cases with advanced liver diseases (5). Approximately 60% of patients with cholestasis require LT before age 18. In adults, approximately 10% of patients require LT, with similar survival rates compared to LT in non-ALGS individuals (5).

Most heart defects require intervention, which may include surgical or radiological arterioplasty in cases of a significant stenosis with compromise of the proximal, lobar, or segmental branches of the pulmonary artery, whereas in a patient with mild or focal compromise, the management can be conservative (5,6). TOF, regardless of whether it is associated with ALGS, requires early intervention to mitigate the poor and fatal outcomes. A substantial cardiac reserve, normally 40% of cardiac output, and a right ventricular/aortic pressure ratio ≤ 0.5 are necessary to be a suitable candidate for LT (4). In case of pulmonary hypertension, cardiac catheterisation with a challenge test with dobutamine can be performed to

simulate the haemodynamic parameters of an LT to identify a significant cardiac disease and manage it before the LT (4,15).

Vascular treatment varies depending on the most important affected sites, which include cerebral vessels, pulmonary arteries, renal vessels, and the mid-aorta. Cerebral manifestations include aneurysm, moyamoya arteriopathy, and dolichoectasia. In symptomatic patients, it is necessary to perform surgical procedures to treat a cerebral aneurysm, whereas a moyamoya arteriopathy needs to be corrected by revascularisation (16). Mid-aortic syndrome requires percutaneous transluminal angioplasty or open surgical correction (17). The aortic conduit reconstruction, compared to a standard arterial anastomosis, was associated with a reduction in the incidence of thrombosis in the hepatic artery (18). Blood vessel abnormalities in the central nervous system require intervention before LT, just as cardiac defects do before the LT procedure (4-6). The skeletal anomalies can be either congenital or secondary to osteopenia caused by cholestasis. Therefore, patients need to take vitamin D supplements, calcium, and phosphorus. Fractures resulting from poor mineralisation must be corrected according to their nature, and their recurrence becomes an indication of LT (19). Finally, therapy with bisphosphonates such as alendronate is recommended to prevent fractures before the LT and after the procedure (6).

Conclusions

Alagille syndrome is a multifaceted genetic disorder, characterised by significant variability in phenotypes and diverse levels of severity. ALGS diagnosis and treatment are a challenge. The social and clinical consequences associated with ALGS make successful conception a rare event. Patients with ALGS and pregnancy must undergo rigorous clinical and paraclinical examinations to differentiate between regular pregnancy diseases, especially those with hepatic and cardiac alterations, and the clinical spectrum of the genetic condition. Individual management is required to improve results. Further studies are needed to determine the actual risks linked to pregnancy and strengthen our knowledge of suitable care for those who are involved.

Declarations

Ethics approval and consent to participate: Informed consent was obtained from the patient before publishing this article. All procedures were performed according to the Declaration of Helsinki.

Availability of data and materials: The data supporting this study are available through the corresponding author upon reasonable request.

Competing interests: The authors declare that they have no competing interests.

Funding: The authors declare that they have received no funding for this report.

Authors' contributions: ARU and DAM: Conceptualization, Visualisation, Writing – original draft. FELP: Methodology, Resources, Writing – review & editing. BANP and LGA: Supervision, Project administration, Writing – review & editing. All authors read and approved the final manuscript.

Acknowledgment: We thank the Research Department of the Hospital Regional de la Orinoquia for their support.

References

1. Diaz-Frias J, Kondamudi NP. Alagille Syndrome. 2023 Aug 12. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. PMID: 29939604.
2. Kohut TJ, Gilbert MA, Loomes KM. Alagille Syndrome: a focused review on clinical features, genetics, and treatment. Semin Liver Dis. 2021;41(4):525-37. Doi: 10.1055/s-0041-1730951. PMID: 34215014.
3. Spinner NB, Loomes KM, Krantz ID, Gilbert MA. Alagille Syndrome. 2000 May 19. In: Adam MP, Feldman J, Mirzaa GM, Pagon RA, Wallace SE, Amemiya A, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993–2025. PMID: 20301450.
4. Ayoub MD, Bakhsh AA, Vandriel SM, Keitel V, Kamath BM. Management of adults with Alagille syndrome. Hepatol Int. 2023;17(5):1098-112. Doi: 10.1007/s12072-023-10578-x. PMID: 37584849, PMCID: PMC10522532.
5. Sanchez P, Farkhondeh A, Pavlinov I, Baumgaertel K, Rodems S, Zheng W. Therapeutics development for alagille syndrome. Front Pharmacol. 2021;12:704586. Doi: 10.3389/fphar.2021.704586. PMID: 34497511, PMCID: PMC8419306.
6. Menon J, Shanmugam N, Vij M, Rammohan A, Rela M. Multidisciplinary management of alagille syndrome. J Multidiscip Healthc. 2022;15:353-64. Doi: 10.2147/JMDH.S295441. PMID: 35237041, PMCID: PMC8883402.
7. Ayoub MD, Kamath BM. Alagille syndrome: diagnostic challenges and advances in management. Diagnostics (Basel). 2020;10(11):907. Doi: 10.3390/diagnostics10110907. PMID: 33172025, PMCID: PMC7694636.
8. Tretter JT, McElhinney DB. Cardiac, Aortic, and Pulmonary Vascular Involvement in Alagille Syndrome. In: Kamath, B., Loomes, K. (eds) Alagille Syndrome. Springer, Cham, 2018, pp. 77-90.
9. Ferrarese A, Senzolo M, Burra P. Successful pregnancy in Alagille Syndrome. Dig Liver Dis. 2015;47(1):86-7. Doi: 10.1016/j.dld.2014.08.047. PMID: 25260494.
10. Morton A, Kumar S. Alagille syndrome and pregnancy. Obstet Med. 2021;14(1):39-41. Doi: 10.1177/1753495X19849738. PMID: 33995572, PMCID: PMC8107961.
11. National Organization for Rare Disease. Alagille Syndrome - Symptoms, Causes, Treatment. NORD [Internet]. 2024. Available at: https://rarediseases.org/rare-diseases/alagille-syndrome/
12. Cheng K, Rosenthal P. Diagnosis and management of

Alagille and progressive familial intrahepatic cholestasis. Hepatol Commun. 2023;7(12):e0314. Doi: 10.1097/HC9.0000000000000314. PMID: 38055640, PMCID:PMC10984671.

13. Mouzaki M, Bronsky J, Gupte G, Hojsak I, Jahnel J, Pai N, et al. Nutrition support of children with chronic liver diseases: a joint position paper of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr. 2019;69(4):498-511. Doi: 10.1097/MPG.0000000000002443. PMID: 31436707.
14. Alicea DS, Santana Felipes R, McLellan BN. Management of refractory pruritus in Alagille syndrome with dupilumab treatment: A case report. JAAD Case Rep. 2024;51:63-5. Doi: 10.1016/j.jdcr.2024.06.030. PMID: 39165631, PMCID: PMC11334727.
15. Smithson S, Hall D, Trachtenberg B, Bhimaraj A, Estep JD, Balzer DT, et al. Treatment of cardiovascular complications of Alagille syndrome in clinical optimization for liver transplantation. Int J Cardiol. 2014;176(2):e37-40. Doi: 10.1016/j.ijcard.2014.04.187. PMID: 25091721.
16. Baird LC, Smith ER, Ichord R, Piccoli DA, Bernard TJ, Spinner NB, et al. Moyamoya syndrome associated with Alagille syndrome: outcome after surgical revascularization. J Pediatr. 2015;166(2):470-3. Doi: 10.1016/j.jpeds.2014.10.067. PMID: 25465847.
17. Salem JE, Bruguiere E, Iserin L, Guiochon-Mantel A, Plouin PF. Hypertension and aortorenal disease in Alagille syndrome. J Hypertens. 2012;30(7):1300-6. Doi: 10.1097/HJH.0b013e3283531e1f. PMID: 22525199.
18. Kohaut J, Pommier R, Guerin F, Pariente D, Jacquemin E, Martelli H, et al. Abdominal arterial anomalies in children with alagille syndrome: surgical aspects and outcomes of liver transplantation. J Pediatr Gastroenterol Nutr. 2017;64(6):888-91. Doi: 10.1097/MPG.0000000000001538. PMID: 28141679.
19. Lee HP, Kang B, Choi SY, Lee S, Lee SK, Choe YH. Outcome of alagille syndrome patients who had previously received kasai operation during infancy: a single center study. Pediatr Gastroenterol Hepatol Nutr. 2015;18(3):175-9. Doi: 10.5223/pghn.2015.18.3.175. PMID: 26473137, PMCID: PMC4600701.