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Pregnancy with chronic liver disorders: maternal and fetal outcomes

Alice Mariana Lima Corredeira

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Estudante:

Alice Mariana Lima Corredeira
alicecorredeira005@gmail.com
Mestrado Integrado em Medicina
Instituto de Ciências Biomédicas Abel Salazar, Universidade do Porto

Orientador:

Dr. António José Costa Lima da Cunha Braga
Assistente Hospitalar no Centro Materno Infantil do Norte, Unidade Local de Saúde de Santo António
Serviço de Obstetrícia do Centro Materno Infantil do Norte, Unidade Local de Saúde de Santo António

Coorientador:

Professor Doutor Luís Guedes-Martins
Assistente Hospitalar Graduado no Centro Materno Infantil do Norte, Unidade Local de Saúde de Santo António
Diretor do Centro de Medicina Fetal, Medicina Fetal Porto
Serviço de Obstetrícia do Centro Materno Infantil do Norte, Unidade Local de Saúde de Santo António

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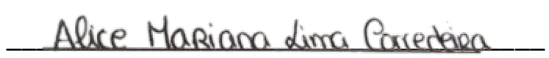
Estudante:



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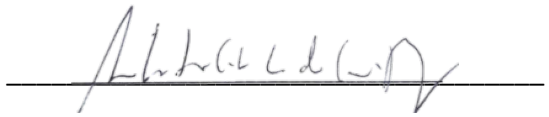

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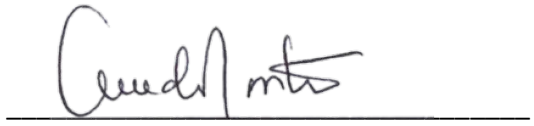

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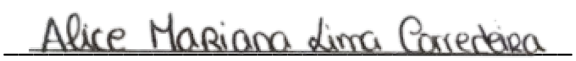
Declaration of Scientific Integrity

I, Alice Mariana Lima Corredeira, student number 201807639 of the Integrated Master's Degree in Medicine of the School of Medicine and Biomedical Sciences of the University of Porto, declare that this dissertation is my own work and has not been previously used in any other course or curricular units, from this or another institution. References to other authors (statements, ideas, thoughts) scrupulously respect the attribution rules and are duly indicated in the text and bibliographical references, per the referencing rules. I am aware that the practice of plagiarism and self-plagiarism constitutes an academic offence.



À minha avó Glória,
cujo amor e dedicação moldaram o meu percurso educativo e que será para sempre fonte de inspiração e uma referência para mim.

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Ao Dr. António Braga, o meu orientador, o meu sincero agradecimento por toda a sua dedicação e ajuda incansável, incentivo constante, compreensão e prontidão para todos os esclarecimentos ao longo deste trabalho.

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Resumo

Introdução: A doença hepática crónica (DHC) caracteriza-se por um conjunto de patologias em que as funções hepáticas se deterioram progressivamente por mais de seis meses, o que pode eventualmente levar ao desenvolvimento de fibrose e cirrose. Aproximadamente 3,00% das mulheres grávidas em países desenvolvidos apresentam alguma forma de doença hepática. Estas patologias podem ser categorizadas em dois grupos distintos: doenças hepáticas específicas da gravidez e doenças hepáticas agudas ou crónicas coincidentes com o período gestacional. A literatura é escassa sobre a gestão e os potenciais desfechos da gravidez em doentes com DHC. Assim, considerando a crescente incidência de mulheres com DHC que tentam engravidar, os diversos riscos e maus resultados que podem enfrentar, e as muitas complicações que podem ocorrer, realizámos um estudo que avaliou retrospetivamente os desfechos e a gestão da gravidez em mulheres com DHC no nosso centro.

Materiais e Métodos: Foi realizado um estudo de coorte retrospetivo, analisando as gravidezes de mulheres com DHC de janeiro de 2007 a dezembro de 2023. Foram registados os desfechos maternos e fetais, bem como informações sobre fármacos utilizados durante a gravidez e o histórico obstétrico. O teste do Qui-Quadrado e o Teste T para Amostras Independentes foram utilizados para comparar o grupo DHC com o grupo de controlo e o grupo de cirrose com o grupo DHC sem cirrose. Foi considerado estatisticamente significativo um valor de $p < 0,05$.

Resultados: Foram analisados os dados de 84 gravidezes de 59 doentes com DHC (G1) e o grupo de controlo (G0) foi composto por 168 gravidezes de mulheres saudáveis. O diagnóstico de DHC está associado de forma estatisticamente significativa à presença de restrição do crescimento fetal (22,53%), menor idade gestacional ao parto (36,82 semanas), menor peso do recém-nascido (2754,38 g) e necessidade de admissão na Unidade de Cuidados Intensivos Neonatais (15,62%). Além disso, as mulheres com cirrose hepática no grupo de estudo apresentaram uma associação estatisticamente significativa com uma taxa mais baixa de nados vivos (42,86%), taxas mais altas de aborto espontâneo (28,57%), de interrupção da gravidez (28,57%) e de complicações no parto (100,00%). Além disso, 36,23% das gravidezes com doença hepática crónica tiveram uma exacerbação, sendo os grupos mais afetados aqueles com cirrose hepática e doenças hepáticas autoimunes.

Conclusões: A gravidez em doentes com DHC representa um aumento do risco de complicações tanto para a mãe como para o feto. As complicações maternas e fetais são ainda maiores em doentes com cirrose. A vigilância da gravidez em doentes com DHC deve ser atenta, seguindo

protocolos rigorosos e conduzida por equipas especializadas para garantir os melhores resultados obstétricos possíveis.

Palavras-chave: Gravidez; Doenças hepáticas; Transplante hepático; Complicações na gravidez; Nascimento prematuro; Aborto espontâneo; Pré-eclâmpsia; Restrição de crescimento fetal

Abstract

Introduction: Chronic liver disorder (CLD) is a condition in which liver functions progressively deteriorate for more than six months, which can eventually lead to the development of fibrosis and cirrhosis. Approximately 3,00% of pregnant women in developed countries experience some form of liver disease. These conditions can be categorized into two distinct groups: pregnancy-specific liver diseases and acute or chronic liver diseases coinciding with the gestational period. Literature is scarce on the management and potential outcomes of pregnancy in CLD patients. Thus, considering the growing incidence of women with CLD attempting pregnancy, the variety of risks and poor outcomes that they may face, and the many complications that can interpose, we conducted a study that retrospectively assessed pregnancy outcomes and management in CLD women in our center.

Materials and Methods: We conducted a retrospective cohort study, analyzing CLD women's pregnancies from January 2007 to December 2023. Maternal and fetal outcomes were recorded, as well as information concerning medications taken during pregnancy and obstetric history. The Chi-Square and the Independent-Samples T-Test were used to compare the CLD group to the control group and the CLD cirrhosis group to the CLD without cirrhosis group. A p-value of <0,05 was considered statistically significant.

Results: We reviewed the data of 84 pregnancies from 59 CLD patients (G1), the control group (G0) was composed by 168 healthy women pregnancies. The CLD diagnosis has a statistically significant association with the presence of fetal growth restriction (22,53%), less gestational age at delivery (36,82 weeks), lower newborn's weight birth (2754,38g) and newborn's need for Intensive Care Unit admission (15,62%). Besides this, women with hepatic cirrhosis among the study group had statistically significant association with the occurence of lower live birth rate (42,86%) and higher rates of miscarriage (28,57%), termination of pregnancy (28,57%) and complications at birth (100,00%). Moreover, 36,23% of pregnancies with chronic liver disease experienced a flare, with the most affected groups being those with hepatic cirrhosis and autoimmune liver diseases.

Conclusions: CLD pregnancy poses an increased risk of adverse pregnancy outcomes for both mother and fetus. Maternal and fetal complications are further increased in patients with cirrhosis. CLD pregnancy surveillance must be stringent, following rigorous protocols, and conducted by specialized teams to ensure the best possible obstetric outcomes.

Keywords: Pregnancy; Liver diseases; Liver transplantation; Pregnancy complications; Premature birth; Miscarriage; Preeclampsia; Fetal Growth Restriction

Abbreviation List

AAT - Alpha-1 antitrypsin
AATD - Alpha-1 antitrypsin deficiency
ACOG - American College of Obstetricians and Gynecologists
AFLP - Acute fatty liver of pregnancy
AIH - Autoimmune hepatitis
ALBI - Albumin-bilirubin
ALP - Alkaline phosphatase
ALT - Alanine transaminase
APGAR - Appearance, Pulse, Grimace, Activity and Respiration
APO - Adverse pregnancy outcomes
ARSA - Aberrant right subclavian artery
AST - Aspartate aminotransferase
ATP - Adenosine triphosphate
CLD - Chronic liver disorder
FGR - Fetal growth restriction
G0 - Control group
G1 - Study group
G1a - Subgroup analysis
GGT - Gamma-glutamyl transpeptidase
GH - Gestational hypertension
HDP - Hypertensive disorders in pregnancy
HELLP - Hemolysis, Elevated Liver enzymes and Low Platelets
ICU - Intensive care unit
ICP - Intrahepatic cholestasis of pregnancy
ICP3 - Intrahepatic cholestasis of pregnancy-3
IGFs - Insulin-like growth factors
LMWH - Low Molecular Weight Heparin
LT - Liver Transplant
MDR3 - Multidrug resistance protein 3
MELD - Model End Stage Liver Disease
MMF - Mycophenolate mofetil
NICU - Neonatal intensive care unit
PBC - Primary biliary cholangitis
PE - Preeclampsia
PFO - Patent foramen ovale
PFIC - Progressive familial intrahepatic cholestasis
PIH - Pregnancy-induced hypertension
PSC - Primary sclerosing cholangitis
SPSS - Statistical Package for the Social Sciences
UDCA - Ursodeoxycholic acid
VLCADD - Very Long Chain Acyl-CoA Dehydrogenase Deficiency

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Introduction

Chronic liver disorder (CLD) is a condition in which liver functions progressively deteriorate for more than six months. These functions include the synthesis of clotting factors and other proteins, detoxification of harmful products of metabolism, and excretion of bile. CLD is a continuous process of inflammation, destruction, and regeneration of liver tissue, which can eventually lead to the development of fibrosis and cirrhosis. There are several causes of chronic liver disease, including prolonged alcohol abuse, exposure to toxins, infection, autoimmune diseases, genetic and metabolic disorders. Cirrhosis is the final stage of chronic liver disease, characterized by disruption of liver architecture, the formation of widespread nodules, vascular reorganization, neo-angiogenesis, and deposition of an extracellular matrix.[1]

During pregnancy, changes in hepatic physiology exert a direct influence on gestational outcomes. Approximately 3% of pregnant women in developed countries experience some form of liver disease.[2] These conditions can be categorized into two distinct groups: pregnancy-specific liver diseases and acute or chronic liver diseases coinciding with the gestational period. With the growing incidence of women of childbearing age presenting with chronic liver disease, there is a significant increase in the number of pregnancies with this association, making it crucial to explore the various risks, potential adverse outcomes, and complications associated with these conditions during pregnancy.[3]

The hepatic pathophysiology during pregnancy involves hormonal and hemodynamic adaptations to meet the demands of the fetus and gestation. [2,4] In women with preexisting CLD, especially in the presence of cirrhosis, the risk of disease decompensation and worsening of portal hypertension is significantly elevated.[3]

To comprehend the complexity of risks and adverse outcomes that women with CLD experience during pregnancy, we focus on the main groups of chronic hepatic pathologies present in our center, deliberately excluding viral hepatitis and pregnancy-specific liver diseases. This approach aims to deepen the understanding of these specific conditions, providing a foundation for targeted management and prevention strategies.

Regarding autoimmune responses directed towards the liver, these may not only independently influence gestation but also exhibit interconnections and overlaps, thereby amplifying clinical complexity. Autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC) stand as the three primary autoimmune liver diseases.

Autoimmune hepatitis (AIH) is a rare chronic inflammatory liver disease that predominantly affects women of reproductive age, thereby increasing its association with pregnancy. It manifests in a spectrum of clinical presentations, ranging from asymptomatic chronic hepatitis

to fulminant acute liver failure. The diagnosis of AIH is primarily exclusionary, posing challenges during pregnancy due to immunological alterations that foster a state of tolerance, leading to improvement in previously diagnosed pregnant individuals and susceptibility to postpartum exacerbations. The progression of pregnancy in AIH patients is influenced by hepatic conditions, comorbidities, and fetal risks related to medication, necessitating a personalized approach involving preconception counseling and multidisciplinary monitoring.[4] Maternal outcomes encompass an increased incidence of gestational diabetes and hypertensive complications. With well-controlled disease, the gestational prognosis is generally favorable, in contrast to challenges associated with recent exacerbations or a lack of therapeutic intervention.[4,5] Fetal outcomes, although typically positive, reveal a higher incidence of preterm births, fetal growth restriction, and dystocic cesarean deliveries, attributed to the pro-inflammatory state of AIH.[4–6]

Primary biliary cholangitis (PBC) is an autoimmune liver disease that primarily affects older women, although up to 25% of cases are diagnosed at childbearing age. During pregnancy, up to one-third of new PBC diagnoses occur, often confused with intrahepatic cholestasis of pregnancy.[5] Despite potential improvements in liver tests during pregnancy, pruritus is common, and in postpartum, approximately 60% of women with PBC experience a disease exacerbation.[6] Regarding fetal outcomes, pregnancies affected by PBC exhibit lower rates of live births and a higher incidence of prematurity. However, a definitive correlation between the extent of maternal serum bile acid and transaminase concentrations and the duration of gestation has not been established.[5]

Primary sclerosing cholangitis (PSC) is an autoimmune hepatic disorder characterized by inflammation and fibrosis in the bile ducts. Associated with inflammatory bowel disease, particularly ulcerative colitis, it can progress to progressive biliary strictures, recurrent bacterial cholangitis, and cirrhosis.[5,6] Diagnosis involves clinical, laboratory, and cholangiographic criteria, marked by the irregularity and diffuse narrowing of the bile ducts. During pregnancy, common symptoms include pruritus and abdominal pain. In women treated with ursodeoxycholic acid (UDCA), hepatic parameters typically remain stable, contrasting with postpartum exacerbations.[5,6] Fetal outcomes involve an increased incidence of preterm births and cesarean deliveries, with no association with fetal growth restriction, stillbirth, congenital malformations, or neonatal deaths.[5–7] It is noteworthy to emphasize that the previously mentioned hepatic immunological disorders may manifest in variant forms known as overlap syndromes, with hepatitis AIH-PBC being the most common, affecting approximately 10% of the adult population diagnosed with these conditions.[5]

Pregnancy poses a challenge for women with specific genetic conditions, necessitating a thorough analysis of their impacts during this period. These hereditary pathologies, each with distinctive characteristics, require a comprehensive assessment during pregnancy.

Alpha-1 antitrypsin deficiency (AATD), a dominant genetic condition, reduces the levels and functionality of alpha-1 antitrypsin (AAT), a protease inhibitor. AAT plays a crucial role in regulating inflammation and the immune response, impacting fertility and embryo implantation.[8] During pregnancy, estrogen induces AAT expression in the liver, resulting in a relative increase in circulating levels. However, these levels do not reach normal values, correlating with miscarriages and an increased risk of preeclampsia due to elevated pro-inflammatory cytokine levels.[8–10] Pregnancies with premature membrane rupture often exhibit significantly reduced alpha-1 antitrypsin activity in the amniotic fluid.[8] In this context, appropriate assessment and management of AATD become crucial to optimizing maternal outcomes throughout pregnancy.

Biallelic variations in hepatobiliary transporter genes are crucial in severe pediatric liver diseases, particularly progressive familial intrahepatic cholestasis (PFIC) syndromes, which result from defects in bile acid transport. Around 25% of women with intrahepatic cholestasis of pregnancy (ICP) have heterozygous mutations in the ABCB4, ABCB11, and ATP8B1 genes, with some having mutations in other cholestasis-related genes.[5] Mutations in the ABCB4 gene, also known as MDR3 (multidrug resistance protein 3), are responsible for about 15% of ICP cases, specifically intrahepatic cholestasis of pregnancy-3 (ICP3).[11] MDR3, a phosphatidylcholine flipase, is essential for proper phosphatidylcholine secretion, and its dysfunction leads to epithelial cell injury and biochemical disruptions key to ICP pathogenesis.[12] Genetic predisposition to ICP is indicated by familial clustering, higher prevalence among first-degree relatives, and significant recurrence rates. Therefore, integrating genetic profiling into prenatal care is recommended for those with a history of ICP or symptoms suggesting a genetic cause.

Wilson's disease is an autosomal recessive inherited hepatic condition arising from mutations in the copper transporter protein ATP7B, leading to excessive copper accumulation in the liver, brain, and eyes. This condition can result in acute liver failure or chronic liver disease, with or without neuropsychiatric manifestations. Due to the association of this pathology with infertility and an increased risk of miscarriage, it is imperative to provide preconception counseling to affected women.[5] Furthermore, it is crucial to emphasize that during pregnancy, maintaining and adjusting chelation therapy is necessary. This is undertaken to optimize positive maternal and fetal outcomes.

Hemochromatosis is an autosomal recessive genetic disorder characterized by iron overload in the body. Women affected by this metabolic disorder face a heightened risk of

manifestations such as preeclampsia and gestational hypertension. Additionally, there is an increased likelihood of fetuses experiencing fetal growth restriction and neurodevelopmental disorders, attributed to elevated lead exposure resulting from this condition.[13]

Very Long Chain Acyl-CoA Dehydrogenase Deficiency (VLCADD) is an autosomal recessive inherited condition characterized by impaired mitochondrial β-oxidation of very long-chain fatty acids. Despite being a rare condition, VLCADD in pregnant women presents challenges in its management due to the scarcity of documented cases and the lack of specific guidelines. It has been observed that women with VLCADD may experience stabilization during pregnancy, attributed to an adaptation in deficient maternal β-oxidation, possibly mediated by the adaptive response of the unaffected placenta and fetus. However, it is important to note that muscular symptoms tend to worsen immediately after delivery, as reported in previously documented cases.[14] This dynamic underscores the need for careful postpartum monitoring and highlights the complexity of the clinical management of this condition during pregnancy. This genetic condition can impact both the fetus and the mother during pregnancy. In affected fetuses, including the placenta, incomplete mitochondrial beta-oxidation redirects substrate metabolism to alternative pathways in peroxisomes and microsomes. Unlike mitochondria, peroxisomal beta-oxidation doesn't produce ATP, generating peroxide radicals and other harmful species, further harming placental mitochondrial function. With adjacent fetal and maternal placental circulations, toxic by-products freely enter maternal circulation, affecting fetal and maternal organs, notably the liver. Cytotoxic fatty acids disrupt liver metabolism, leading to microvesicular steatosis and mitochondrial dysfunction, contributing to acute fatty liver of pregnancy (AFLP) pathogenesis.[15,16]

Cirrhosis in women of reproductive age, although uncommon, is associated with infertility. Preconception evaluation in this group of patients must be individualized, and requires risk assessment, with MELD <6 and pre-conception ALBI <-2.7 indicating better outcomes, whereas MELD >10 and higher ALBI are associated with hepatic decompensation and gestational complications.[5] In the presence of portal hypertension, the expansion of blood volume during pregnancy increases the risk of variceal bleeding, which is more prevalent in the second and third trimesters.[6] Risk assessment for bleeding includes upper gastrointestinal endoscopy, preferably pre-conceptionally and during the second trimester. In cirrhotic pregnancies, there is a higher obstetric risk compared to the general population, often favoring vaginal delivery, with a reduction in the duration of the second stage of labor to minimize the increased intravenous pressure associated with maternal Valsalva efforts.[5,6]

Budd-Chiari Syndrome, characterized by obstruction or thrombosis of the hepatic veins, results in increased pressure in the hepatic sinuses, triggering complications such as ischemia,

portal hypertension, and hepatic necrosis.[6] During pregnancy, the elevation of pro-coagulant activity and reduction in anticoagulants contribute to the development of hepatic vascular diseases. The diagnosis is associated with high rates of adverse events, including miscarriages, preterm births, cesarean deliveries, stillbirths, HELLP syndrome, and bleeding from esophageal varices.[5] Thrombotic event prevention involves the use of low-molecular-weight heparin throughout pregnancy, combined with preconception counseling and appropriate multidisciplinary monitoring, highlighting the interconnection of this syndrome with hepatic pathologies and portal hypertension in pregnant women.[5,6]

Pregnancy in women who have undergone liver transplantation presents a unique clinical scenario, involving considerations related to the graft, immunosuppressive therapy, and the physiological adaptations inherent to pregnancy.

In women who have undergone liver transplantation, it is advisable to postpone pregnancy for at least one to two years post-transplant to reduce the risks of obstetric complications attributed to potential acute organ rejection.[5,6] Systematic assessments are recommended due to the propensity for maternal gestational disorders such as hypertension, preeclampsia, gestational diabetes, cholestasis, and acute kidney injury.[5] During pregnancy, the suspension of immunosuppression and changes in plasma volume increase the likelihood of acute cellular rejection, underscoring the importance of regular monitoring and therapeutic adjustments to ensure adequate control. While postpartum bleeding rates are higher, antepartum rates remain comparable to the general population.[5] Fetal outcomes indicate variable rates of live births, miscarriages, and stillbirths, associated with increased rates of prematurity and fetal growth restriction. Prenatal care is crucial, and although there are no specific contraindications for vaginal delivery, cesarean sections are more frequent than in the general population, highlighting the need for an individualized approach in this complex clinical context.[5]

In the face of these pathophysiological complexities, pregnancy in women with CLD demands a careful approach. Multidisciplinary management emerges as essential to ensure favorable maternal and fetal outcomes, emphasizing the need to recognize and mitigate the specific risks associated with this medical condition during pregnancy.

In summary, the various aforementioned chronic liver disorders require a differentiated clinical approach during pregnancy, aiming to understand the interconnection between changes in hepatic physiology during gestation and the impact of these diseases on the maternal-fetal dyad.

Materials and methods

This retrospective, observational cohort study was carried out at Centro Materno-Infantil do Norte, Unidade Local de Saúde de Santo António in Porto, Portugal. The study's protocol was approved by the institutional Ethics Committee, the Department of Clinical Investigation and the Learning, Formation and Investigation Department – 2023,228 (188-DEFI/180-CE).

The studied population consisted of all pregnant CLD patients who received obstetric care, in our center, from January 2007 to December 2023. Only women with documented pregnancy outcomes were deemed eligible for inclusion in the study. Preexisting chronic liver disease within the study cohort was defined to encompass autoimmune hepatitis, primary biliary cholangitis, alpha-1-antitrypsin deficiency, progressive familial intrahepatic cholestasis (PFIC), Wilson´s disease, very long-chain acyl-CoA dehydrogenase deficiency (VLCADD), cirrhosis and portal hypertension, Budd-Chiari syndrome and history of liver transplantation. Pregnancy-specific liver diseases, such as hyperemesis gravidarum, acute fatty liver of pregnancy, intrahepatic cholestasis of pregnancy, hemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome, were excluded from the study. Additionally, viral hepatitis, as well as, terminations for personal reasons were also excluded.

Multifetal gestations were excluded from the study. Each pregnancy was considered an event. Our sample comprised a total of 84 pregnancies from 59 with CLD patients. The control group consisted of 168 healthy pregnant patients with low-risk singleton pregnancies, selected randomly at a ratio of 1:2, who were followed at our institution during the same period.

Data was retrived from the patients' clinical files. Information regarding the following parameters was collected in both groups: maternal age, past medical and obstetric history, pre and pregnancy medication and maternal, obstetric, and perinatal outcomes. In the study group, CLD-related data were also collected: CLD evolution time, current and cumulative manifestations and previous clinical and laboratory criteria for CLD. Furthermore, liver parameters such as pregnancy flare and postpartum flare, as well as the presence of anemia, thrombocytopenia, infection, and cholestasis were also collected.

Concerning analytical profile during pregnancy, anemia was defined as hemoglobin or hematocrit levels below 11 g/dl and 33%, respectively, in the first and third trimester, and below 10.5g/dl and 32% in the second one. Thrombocytopenia was defined as a platelet count below the lower limit of the normal range (typically, <150,000 /microL). Cholestasis has been defined as the presence of pruritus associated with analytical alterations in the hepatic profile.

Regarding Obstetric outcomes, we retrieved data concerning gestational hypertension, gestational diabetes mellitus, preeclampsia, fetal growth restriction (FGR), live birth ratio,

pregnancy miscarriage, termination of pregnancy, preterm delivery, gestational age at delivery and cesarean section. Perinatal outcomes included Apgar score at 5 minutes, birth weight, admission to the neonatal intensive care unit, complications at birth and fetal malformations.

Diagnosis of liver cirrhosis was considered confirmed when based on biopsy findings or imaging combined with laboratory findings. The monitoring of the disease during pregnancy was assessed through liver function, measured by AST and ALT. Flare was considered as either new signs of active disease by clinical and laboratory variables (twofold increase in serum transaminases and appearance of symptoms), escalation in therapy or change in the physician global assessment.

APO as a composite outcome was defined as the occurrence of miscarriage, stillbirth, preterm delivery, fetal growth restriction, placental abruption and/or development of hypertensive disorders of pregnancy (HDP - gestational hypertension/preeclampsia/HELLP syndrome). Miscarriage was defined as the involuntary loss of a fetus before the 20th week of gestation and stillbirth as the death of the fetus beyond the 20th week of pregnancy. Preterm delivery was defined as a birth that occurs between 20 0/7 and 36 6/7 weeks of gestation.[17] Fetal growth restriction was defined as an estimated fetal weight less than the 10th percentile for gestational age, using the curves defined for the Portuguese population.[18]

Hypertensive disorders of pregnancy were defined according to the 2019 American College of Obstetricians and Gynecologists Committee (ACOG) criteria.[19] Gestational hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, or both, on two occasions at least 4 hours apart after 20 weeks of gestation, in a woman with previously normal blood pressure in the absence of proteinuria or organ dysfunction, and that returns to normal in the postpartum period.[19] Preeclampsia was also defined according to the ACOG criteria, as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with previously normal blood pressure and proteinuria. In the absence of proteinuria, preeclampsia was defined as new onset hypertension with new onset of target organ damage (platelet count less than 100x 109/L; serum creatinine concentration greater than 1.1 mg/dL or doubling of the serum creatinine concentration in the absence of other renal disease; elevated blood concentrations of liver transaminases to twice the upper limit of normal concentration; severe persistent right upper quadrant or epigastric pain and not accounted for by alternative diagnoses; pulmonary edema or new-onset headache unresponsive to acetaminophen and not accounted for by alternative diagnoses; or visual disturbances). Occurrence of new-onset tonicclonic, focal, or multifocal seizures in the absence of other causative conditions established the diagnosis of eclampsia.[19]

Gestational diabetes mellitus was defined as onset or first recognition of abnormal glucose tolerance during pregnancy. The diagnosis was made if the fasting glucose level was higher than 92 mg/dL during the first trimester or if there was at least one abnormal value at the oral glucose tolerance test, undertaken at 24–28 weeks of gestation.

Data analysis was performed using the Statistical Package for the Social Sciences, version 29 (SPSS Inc., Chicago, IL, USA). Categorical variables were described in terms of frequency and percentage. Continuous numerical variables were expressed as mean and standard deviation. When applicable, the Chi-Square Test was used to analyze categorical variables. Independent-Sample T-Tests were used to analyze continuous numerical variables. A *p*-value of less than 0,05 was considered statistically significant.

This study used a retrospective, observational design, and it was approved by the Medical Ethical Committee of our center. All patient information remained confidential.

Results

We reviewed the data of 84 pregnancies from 59 CLD patients followed at Centro Materno Infantil do Norte between January 2007 and December 2023. The control group (G0) was composed of 168 healthy women pregnancies, followed at our center during the same period.

Demographic and Clinical Characteristics

Regarding the etiology of chronic liver disorders within the study group, 38 of them (45,24%) had undergone liver transplant, 21 patients (25,00%) exhibited autoimmune diseases, 18 (21,43%) presented with genetic diseases, and 7 (8,33%) had liver cirrhosis and portal hypertension. (Table I)

In the study group, there were 70 pregnancies resulting in live births, which accounts for a rate of 83,33%. Out of the pregnancies of women with CLD, 25 (36,23%) experienced a flare. The number of pregnancies with flares was higher during pregnancy (29,87%) as compared to the postpartum period (15,94%). The third trimester had the highest number of occurrences (68,97%). The incidence of flares was higher in patients with cirrhosis, and autoimmune liver diseases. (Table II)

The mean maternal age in the study group was 32,42 years (± 5,87) while it was 31,69 years (± 5,50) in the control the study group, 37 were primiparous (primigravida). (Table II and III)

When analyzing obstetric backgrounds in both groups, a statistically significant association was found: 64,06% of patients in the CLD group had a history of an adverse obstetric event (APO), versus 16,67% of patients in the control group ($p<0,05$). The highest results were observed in pregnant women with cirrhotic pathology. (Table II)

Among CLD patients, the minimum week of gestation they were in by the time they gave birth was the thirtieth, the maximum was the fortieth week, and the mean was 36,82 (±2,60) weeks. On the other hand, in the control group, the mean week of gestation reached was 38,14 (±2,03), the minimum was 31 weeks, and the maximum was 41 weeks ($p<0,05$).

In the study group, the mean age at diagnosis of chronic liver disorder was 22,89 years (± 9,29). Excluding pregnancies post-liver transplantation, the duration of disease prior to pregnancy was 9,04 years (±6,89). In the subgroup of liver transplant recipients, the average time interval between transplantation and pregnancy was 6,53 years (± 4,76). (Table III)

Pregnancy Surveillance

Regarding CLD medications, 77,78% of patients were on hepatic medication at the time of conception. In Group 1 (G1), tacrolimus was the most prescribed medication at 34,57%, followed

by prednisolone at 23,46%, azathioprine at 18,52%, and cyclosporine at 16,05%. Ursodeoxycholic acid (UDCA) was used in 4,94%, cholestyramine and hydroxychloroquine in 3,70%. Mycophenolate mofetil (MMF) was prescribed in a single pregnancy (1,23%) that resulted in miscarriage. (Table IV)

Among the patients taking medication, 23,53% had to increase the dosage, and approximately 34,33% changed their medication during pregnancy. Pregnant women in the CLD group received aspirin in 70,23% of cases, and 23,80% of patients in this group were treated with low molecular weight heparins (LMWH). (Table V)

Obstetric Outcomes

Regarding pregnancy complications, the number of patients who developed gestational hypertension wasn`t higher in the CLD group (1,45%) in comparison to G0 (3,57%). The same applied to the development of gestational diabetes, where 5,71% of patients in the study group developed this condition, versus 7,14% of patients in the control group, and with preeclampsia, 1,41% of the patients with CLD developed this condition in comparison to G0 (2,98%).

Regarding patients who developed fetal growth restriction, the number was significantly higher ($p<0,05$) in the CLD group (22,53%) in comparison to G0 (5,36%). In the study group, there were 7 miscarriages (8,54%) and 7 terminations of pregnancy (8,54%), while none were registered in the control group.

When it came to preterm delivery, 21,43% of the CLD patients and 12,50% of the patients in the control group suffered from it.

Concerning the cesarean section prevalence, in the control group, 38,09% of pregnancies ended in a cesarean, while in the study group, that outcome was present in 39,71% of pregnancies, there was no statistically significant difference.

No maternal deaths occurred. (Table VI)

Perinatal Outcomes

When it came to the results concerning the newborn, we verified that in the control group, the mean Apgar value five minutes after the delivery was 9,71 (±0,66), and in the study group, it was 9,52 (±0,70). The mean weight at birth in the control group was 3031,52 (±523,17) grams, and in the study group, it was 2754,38 (±528,24) grams, translating into a statistically significant difference ($p<0,05$) between these two groups, with the babies from mothers with CLD being considerably lighter.

Regarding the need for admission to an intensive care unit, 6,58% and 15,62% of the newborns required this type of care in G0 and G1, respectively (p<0,05). No significant differences were observed in fetal malformations and birth complications between the two groups.

There were no stillbirths. (Table VII)

Subgroup analysis

G1a: Pregnant women with liver cirrhosis and portal hypertension vs without liver cirrhosis and portal hypertension

In this sub-analysis of the study group, we will be comparing patients with liver cirrhosis and portal hypertension with those without it. The mean maternal age for patients with liver cirrhosis was 33,71 years (± 4,11), while for patients without liver cirrhosis, it was 32,30 years (± 6,00). However, there was no significant difference between the groups. (Table VIII)

Focusing on obstetric outcomes, out of all the pregnancies that reached the 37th gestational week, only three were cirrhotic. All three of these term pregnancies resulted in live births, where in the non-cirrhotic group 87,01% of the term pregnancies resulted in live births. Only 42,86% of the cirrhotic pregnancies resulted in live births. The same trend was observed in miscarriage, which was significantly higher (p<0,05) in the cirrhotic group (28,57%) compared to the non-cirrhotic group (6,66%). Similarly, termination of pregnancy (p<0,05) was more common in the cirrhotic subgroup (28,57%) compared to the non-cirrhotic subgroup (6,66%). Preterm delivery occurred in 22,38% of patients with non-cirrhosis, compared to none in the cirrhotic group. Only 1 out of the 3 (33,33%) cirrhotic term pregnancies had growth fetal restriction, compared to 20,89% in non-cirrhotic pregnancies. (Table IX)

In perinatal outcomes, complications at birth were statistically higher (p<0,05) in the cirrhosis group, where all pregnancies with live births experienced complications (100%), compared to non-cirrhotic pregnancies (26,31%). (Table X)

In terms of analytical parameters, all term cirrhotic pregnancies had pregnancy cholestasis (100%), compared to non-cirrhotic pregnancies, where it was only 18,66%, a statistically significant difference. There were no statistically relevant differences in the remaining analyzed parameters (anemia, thrombocytopenia, and infection). (Table XI)

Regarding flares during pregnancy, the incidence was 100% in the cirrhotic group, significantly different from the non-cirrhotic group (27,03%). On the other hand, there was no significant difference between the two subgroups in terms of flares postpartum. (Table XI)

Discussion

Demographic and Clinical Characteristics

In our study, we observed an apparent lack of correlation between maternal age at conception and the presence of chronic liver disease in pregnant women. This finding, based on the inclusion of 84 women with this specific condition, whose mean age at conception was 32,42 (±5,87) years, did not reveal significant differences when compared to the healthy control population. This phenomenon contradicts the initial expectation that maternal age at conception would be more advanced among women with chronic liver disease, compared to their healthy counterparts.[20] Such results corroborate previous findings in the scientific literature[21,22], suggesting that various factors, including advances in medical care, specialized monitoring, and conscientious family planning, may influence the decision to conceive and the optimal timing to do so, regardless of the presence of chronic disease. A multidisciplinary and informed approach can empower women with chronic liver disease to make reproductive choices that meet their individual needs and reduce risks during pregnancy. It is crucial to consider not only the patient's clinical condition but also psychosocial and reproductive health aspects when planning and monitoring pregnancy in these circumstances. However, when analyzing the age of pregnant women with cirrhotic liver pathology compared to non-cirrhotic liver pathology, it was found that maternal age was higher in those with cirrhosis.

It was observed that in the group of women with chronic liver disease, there was a higher proportion of primiparous women, whereas in the group of healthy women, there was a higher proportion of multiparous women, which is consistent with the literature.[20,21,23] The difference in rates of primiparity and multiparity between women with and without chronic liver disease reflects a complex interplay of awareness regarding pregnancy risks, medical counseling, and fertility. Women with chronic liver disease may postpone their first pregnancy due to health considerations and receive tailored guidance, contrasting with women without the condition who are more inclined to have multiple pregnancies. This discrepancy underscores the direct impact of hepatic health on reproductive choices and pregnancy experiences. Additionally, since liver conditions can influence fertility, affected women may pursue pregnancy sooner or face challenges in conceiving again, emphasizing the necessity of holistic consideration of these factors when addressing the reproductive requirements of women with chronic liver disease.

The most prevalent chronic liver pathology in our study sample was liver transplantation, which is a common procedure at our center, serving as a reference for this type of intervention. The primary indication for transplantation was familial amyloidosis polyneuropathy, an endemic condition in our country.

Obstetric Outcomes

Live Births

It has been observed that chronic liver disorders can significantly reduce the rate of live births compared to the control population. However, the methodology of our study involved selecting pregnant women only from the delivery room, which led to an overestimation of the percentage of live birth rates in the control group**.** For this reason, the live birth rate in our study is likely similar to what is expected for the general population. Therefore, although we have different and significant statistics, when interpreting the results of our study based on this information, we can assert that the live birth rates of pregnant women with CLD are similar to those of the general population, except for cirrhotic pregnancies, where the rate of 42,86% reveals that this pathology negatively influences fetal survival.

Our study revealed live birth rates of approximately 90,48% in patients with autoimmune disease, which, while significantly lower than the general population, are considered favorable rates. This finding is consistent with the literature, which reports rates exceeding 77,00%.[24–26]

Solid organ transplants inherently entail pregnancy-related risks. However, our results demonstrate a high rate of live births following liver transplantation, indicating that successful outcomes can indeed be achieved in these women. Recent research suggests that successful transplants allow women to conceive and have healthy offspring, advising a waiting period of one to two years post-transplant before pregnancy. Pregnancies within the first year post-liver transplantation are associated with elevated risks for adverse outcomes in maternal and fetal health, including increased rates of very low birth weight infants, reduced birth rates, increased vulnerability to prematurity, and a heightened risk of graft rejection.[27,28] Our research revealed that the average time between liver transplantation and conception, known as the transplant-to-pregnancy interval, was 6,53(±4,76) years. Within our sample, two individuals became pregnant just one year after their liver transplant, which is a remarkably short interval. Interestingly, both cases did not exhibit an increase in obstetric and fetal complications, which is contrary to what previous studies have shown. Our findings suggest a significantly lower success rate in conception and childbirth for women with a history of liver transplantation compared to the general population, aligning with prior research and meta-analytical results.[29] However, over the past three decades, there has been a progressive improvement in live birth rates, increasing from 60,00% before 1997 to 84,00% between 2007 to 2016.[30]

Gestational Hypertension and Preeclampsia

Li et al. studied the association between normal liver enzyme levels in early pregnancy and the risk of gestational hypertension (GH) and preeclampsia (PE).[31] Their findings suggest that elevated levels of ALT, ALP and GGT within normal limits during early pregnancy are associated with increased risk of GH and PE, indicating a potential role of hepatobiliary function in their development. Monitoring liver enzyme levels early in pregnancy can help identify women at higher risk of these conditions, enabling early prevention strategies.

Medical research has found that individuals with cirrhosis may be more susceptible to hypertensive complications than those in the general population.[23] The incidence of pregnancy-induced hypertension (PIH) has been reported to range from 5.40% to 21.50% in various studies[32], but comparisons with control groups indicate that patients with cirrhosis exhibit higher rates of PIH. Nevertheless, our study findings diverge from this observation, as we did not detect any occurrences of gestational hypertension within our study group. This is in agreement with a population-based cohort study conducted in Sweden, which demonstrated no increased risk of preeclampsia in pregnant women with cirrhosis compared to the general population.[33]

In autoimmune diseases, statistically significant differences in these variables compared to the control group were not observed. This contrasts with reports in the literature[34–36], where autoimmune diseases are associated with higher rates of gestational diabetes as well as hypertensive pregnancy complications, both in women receiving immunosuppression and those not undergoing therapy during pregnancy. The discrepancies in the results compared to our study can probably be attributed to the increased use of aspirin in patients with autoimmune diseases.

Although most studies report a higher rate of gestational hypertension in organ transplant recipients, our study only observed this condition in one pregnant individual, similar to findings in a recent study evaluating outcomes at a single affiliated tertiary transplant center in Turkey.[27] It is noteworthy that these results vary depending on the immunosuppressive therapy utilized. Previous studies have indicated rates of 22,00-29,00% with corticosteroids, 63,00-73,00% with ciclosporin, and 47,00-54,00% with tacrolimus.[5] This aligns with our findings, as the pregnant individual in our study was under ciclosporin therapy during gestation. In our investigation, we observed a notably lower incidence of preeclampsia, at 3,23%, among pregnant liver transplant recipients, in contrast to previous studies reporting rates ranging between 21,00% and 26,00%.[30,37,38] This disparity in outcomes can be attributed to the administration of aspirin

therapy to the pregnant cohort in our study; as a consequence, the prophylactic use of aspirin correlated with a significant reduction in the occurrence of preeclampsia among this population.

Gestational Diabetes

Cirrhosis can induce insulin resistance due to liver dysfunction, leading to elevated blood glucose levels. During pregnancy, placental hormones contribute to insulin resistance, which may be exacerbated in women with liver cirrhosis. Consequently, there is an increased risk of developing gestational diabetes during pregnancy in women with this condition.[39] However, despite literature indicating a higher incidence of gestational diabetes in cirrhotic patients[21,23,32,33,40], our study found no significant difference between pregnant women with cirrhosis and those without. No cases of gestational diabetes were reported in our study cohort.

Calcineurin inhibitors, particularly tacrolimus, are recognized for their association with glucose intolerance. The incidence of gestational diabetes in pregnant LT recipients, as reported in previous studies, ranges from 0% to 11,00%.[27,41] This variability may stem from factors such as sample size, ethnicity, and inclusion of patients with preexisting diabetes. Our study included screening all the patients for insulin resistance, and we found only one patient with gestational diabetes mellitus. It is possible that this occurrence was due to the limited size of our sample, but we also found that this pregnant patient was undergoing tacrolimus therapy. However, we cannot conclusively determine the role of this pharmacological agent in inducing diabetes, as other pregnant individuals were also under this therapy without experiencing any changes in glucose analytical parameters during pregnancy. Recent studies suggest that UDCA may influence glucose homeostasis and insulin resistance. Nonetheless, based on the data from our sample, we cannot draw conclusions regarding the anti-diabetogenic properties of this agent.[42]

It is noteworthy that, despite the commonly observed association between the use of immunosuppressants post-liver transplantation and an increased incidence of gestational diabetes, our findings did not support this assumption. This observation does not appear to be solely a consequence of the limited size of our sample but also suggests a potential influence of underlying liver deficiency in the patients under study. It is plausible that these patients exhibit residual liver deficiency, impacting their ability to perform normal metabolic processes such as neoglucogenesis and glycogenolysis. This liver deficiency may, to some extent, protect these women against the development of gestational diabetes, as their glucose regulation capacity may be compromised even before transplantation. Such conclusions emphasize the importance of considering the liver status of the patient when assessing the risk of gestational complications post-liver transplantation.

Fetal growth restriction

During pregnancy, liver cirrhosis can lead to a series of complications that restrict fetal growth. This begins with impaired placental transport due to compromised hepatic blood flow, reducing the delivery of vital nutrients, oxygen, and hormones to the fetus. Maternal nutritional deficiencies are also common due to poor nutrient absorption and inadequate protein synthesis linked to liver cirrhosis, directly impacting fetal development. Furthermore, hormonal changes, such as altered levels of insulin-like growth factors (IGFs) associated with liver cirrhosis, can disrupt proper fetal growth. Consistent with the findings of our study, several previous studies[32,43] have reported higher rates of fetal growth restriction in pregnant women with liver cirrhosis compared to the general population. However, more recent studies have reported that the differences between the two groups are not significant.[21,33]

There is evidence to suggest that the risk of fetal growth restriction or small-for-gestational-age newborns is higher in patients with autoimmune hepatitis (AIH). Although various definitions of fetal growth restriction have been used in studies, the analysis of newborn weight or estimated fetal weight showed a higher incidence of fetal growth restriction in patients with AIH.[4,44] This finding is consistent with the results of our study.

Regarding the parameter of fetal growth restriction in the group of transplant patients, although the data concerning pregnant individuals were higher than those observed in the control group (12,90% vs. 5,36%, respectively), these differences were not statistically significant. In literature, rates of FGR in liver transplant recipients range between 5,00% and 20,00%.[41] This variability is likely attributed to inconsistent definitions of FGR across studies. Several previous publications have indicated that LT recipients exhibit statistically higher rates of FGR compared to the general population.[41]

Miscarriage and pregnancy termination

In general, our study demonstrated that pregnant women with chronic liver disorders exhibited higher rates of miscarriage compared to the control population. Among women with chronic liver disease, those with cirrhosis experienced the highest number of cases, suggesting a direct association between this underlying condition and this obstetric outcome. However, it is important to note that in the control group, the number of miscarriages may be underreported. In our setting, early miscarriages occurring in the general healthy population are typically not managed in tertiary centers. In both miscarriages and terminations of pregnancy in women with cirrhosis, we observed a similar percentage of cases (28,57%), which were higher than those reported in the general population. This finding aligns with the majority of previous

studies[40,45] and with the association between higher rates of miscarriage in women with chronic diseases. Furthermore, these patients often conceive unintentionally, which may account for the frequency of pregnancy terminations within this cohort.

Within our cohort of women with autoimmune pathology, we recorded 2 cases of miscarriage (9,52%) and no instances of termination of pregnancy. Upon comparing these values with the control population in our study, we observed a heightened incidence, albeit lower than reported in recent literature.[44,46] Concerning patients diagnosed with autoimmune hepatitis, available data present conflicting outcomes. While some authors indicate an elevated risk of miscarriage in AIH patients, a population-based study failed to substantiate these prior findings.[47] Consequently, the rate of miscarriage in AIH patients appears akin to that of the low-risk pregnancy cohort.

Women who have undergone transplantation tend to experience more complications such as miscarriage or elective termination of pregnancy compared to the general population. The rate of miscarriage among LT recipients is estimated to be approximately 11,00-19,00%.[41] In our institution, the incidence of miscarriage was comparatively lower at 7,89% when contrasted with findings from Deshpande et al.'s extensive meta-analysis, which reported a miscarriage rate of 16,00%.[29] In our study, a higher rate of elective termination of pregnancy was observed among women following liver transplantation (14,29%) compared to previous studies, which reported rates of approximately 5,7%[48]. This increase is predominantly due to prenatal diagnoses of familial amyloid polyneuropathy, a condition for which our hospital serves as a referral center.

Preterm birth

In our study, we found no cases of preterm pregnancies among pregnant women with cirrhosis, which is different from previous research showing a higher prevalence of preterm deliveries in this population compared to the control group.[21,23,33]. However, it's important to note that our study sample consisted of only three pregnant women who completed their pregnancies to term, delivering at 37 weeks of gestation. This suggests favorable outcomes and careful monitoring, which allowed for labor induction at 37 weeks.

We confirmed findings from other studies showing an increased risk of preterm birth in women with autoimmune diseases, with our results even surpassing those described in most studies (6-20%).[4,44] In patients with autoimmune hepatitis, the most commonly reported obstetric complication is preterm birth. Consistent with the Swedish study by Stokkeland et al[34],

we found a more than threefold higher risk for preterm birth, which can be justified by the pro-inflammatory state characterizing the pathophysiology of autoimmune hepatitis.

Prior research indicates that liver transplant recipients have a heightened incidence of preterm deliveries compared to the general population, with rates ranging from 14,00% to 53,00%.[27,49] . In a recent meta-analysis by Prodromidou et al., the rate of preterm delivery among liver recipients was reported as 32,00%, and this elevation in preterm delivery rates was attributed to a higher prevalence of prenatal complications in these patients, such as preeclampsia.[49] Although not statistically significant, our study found that five patients delivered before the 37th gestational week, resulting in a preterm delivery rate of 16,67%, consistent with previous findings and possibly linked to the high incidence of obstetric adverse events.

Cesarean section

During the study, although not statistically significant, it was observed that two out of three-term pregnancies in cirrhotic women underwent cesarean section. Previous studies in the literature have shown higher rates of cesarean sections compared to the general population.[21,23,33] Pregnancies complicated by cirrhosis require careful consideration of delivery methods. Both cesarean section and vaginal delivery have advantages and disadvantages, with the choice depending on individual circumstances and hospital policies. Cesarean sections may increase bleeding risk, while vaginal delivery can raise intra-abdominal pressure and the risk of variceal bleeding. Our institutional approach favors cesarean sections only for obstetric indications, with assisted vaginal deliveries and abbreviated second stages of labor considered viable alternatives. However, the decision-making process is complex, and individualizing the decision based on the overall clinical status and severity of cirrhosis underscores the importance of a multidisciplinary approach to optimize maternal and neonatal outcomes in complex pregnancies.

The data on cesarean section did not reveal any significant differences in the autoimmune subgroup compared to the control group, although they occurred at a higher percentage, which is consistent with the results of prior studies.[34,44,46] It is important to determine the mode of delivery based on obstetric indications, and in our group of patients, all cesarean sections were performed based on such indications.

In our study, 11 infants (39,29%) born to women who underwent liver transplantation were delivered by cesarean section. Deshpande et al. conducted a meta-analysis and reported a cesarean section rate of 45,00%, compared to 32,00% in a similar population in the United States.[29] Liver transplant recipients have cesarean delivery rates two to three times higher than

those in the general population. Although most studies on pregnancy following organ transplantation reveal a higher prevalence of cesarean delivery compared to healthy women, it's important to note that vaginal delivery is not contraindicated. The elevated rates of cesarean deliveries may stem from the increased occurrence of obstetric adverse events that occur in this group of patients, leading to more indications for cesarean deliveries.

Perinatal outcomes

Birth weight

Although in the majority of chronic liver disorders, the fetal birth weight has been statistically lower, specifically in the subgroup of cirrhotic patients, this difference was not observed. Due to the pathological condition contributing to hemodynamic disturbances that may compromise uteroplacental blood flow, resulting in reduced nutrient and oxygen delivery, fetal development may be inadequate, leading to low birth weight. Additionally, progressive liver insufficiency influences the synthesis of liver proteins, contributing to vascular homeostasis and adequate placental perfusion. Most studies define the variable of low birth weight (<2,500 g) and report higher rates of low birth weight compared to the general population.[21,33] The study Salman et al. reported a mean birth weight of 2303 ± 981g[50], lower than that demonstrated in our study (2686,67 ± 420,99g). It is important to note that birth weight depends on gestational age and does not truly reflect pathological growth. Assessment of fetal growth restriction, whose definition has evolved over the years, is a more accurate method of evaluation. However, Flemming et al. recently demonstrated that pregnancies in women with cirrhosis are independently associated with large for gestational-age infants, rather than a significant increase in small for gestational-age infants.[23] Nevertheless, these findings were not corroborated by other publications or by our study.

In autoimmune liver disease, lower birth weight (2499,71g) was observed, aligning with previous studies indicating a higher incidence of neonates with low birth weight (<2500,00g) compared to the general population.[34] This association may be attributed to inflammation affecting placental function, potentially leading to chronic villitis and restricting fetal growth. Furthermore, the correlation between autoimmune hepatitis and preterm delivery could contribute to the observed lower birth weight in offspring.

Similarly, in pregnant women who underwent liver transplantation, birth weight was significantly lower compared to the control group (2825,00 g vs. 3031,52 g, respectively). These findings mirror those reported by Deshpande et al.[29], who found a markedly lower mean birth

weight for liver transplant recipients (2866,00 g) compared to the general United States population (3298,00g).

Complications at birth and Admission to neonatal intensive care unit

In pregnant women with cirrhosis, a significant incidence of perinatal complications was observed in previous studies[23], including neonatal jaundice, meconium aspiration, and neonatal respiratory distress. Nonetheless, none of the newborns in our study required admission to the neonatal intensive care unit (NICU), implying that while maternal cirrhosis escalates the risk of perinatal complications, the necessity for NICU admission may not be as prevalent.

Furthermore, pregnant women with autoimmune liver diseases also encountered perinatal challenges, such as neonatal distress syndrome, aligning with prior research. The study underscored the significance of monitoring neonatal health outcomes in pregnancies complicated by maternal liver diseases, particularly evidenced by the occurrence of neonatal sepsis, albeit at a lower rate than reported by Fischer et al. in congenital infections.[46]

Previous studies in transplanted pregnant women delineated respiratory complications and neonatal jaundice necessitating phototherapy[51], akin to the patterns observed in our study. However, the literature accentuates a significant disparity in NICU admission rates post-maternal liver transplantation compared to our findings, suggesting perinatal outcome variations and emphasizing the imperative of further investigation to better elucidate this discrepancy. These findings accentuate the intricacy of perinatal care in pregnancies affected by maternal liver conditions, underscoring the necessity for a multidisciplinary approach and ongoing research endeavors aimed at enhancing comprehension and management of these clinically challenging scenarios.

Fetal malformations

In cirrhosis, previous studies have reported an incidence of congenital malformations ranging from 0,40% to 3,00%.[33,52] However, the specific types of malformations were not specified, and the rates did not differ significantly from those reported in non-cirrhotic pregnancies.

Similarly, in cases of autoimmune liver disease, our study identified specific congenital malformations, including congenital pulmonary valvular atresia and restrictive apical ventricular septal defect with patent foramen ovale (PFO). Nevertheless, no association was found between the incidence of fetal malformations and the presence of autoimmune pathology in pregnant women, aligning with previous research.[34,44]

Regarding liver transplant recipients, while various congenital anomalies have been documented in neonates, our study observed only one case of congenital malformation - an aberrant right subclavian artery (ARSA). Despite challenges in determining the cause of these anomalies, whether due to immunosuppression or genetic predisposition, studies have reported no significant differences in the rate of malformations between LT recipients and the general population.[41]

Thus, while specific congenital malformations may vary across different liver pathologies, overall, the incidence of these anomalies appears to be comparable to that observed in the general population.

Genetic liver diseases

Our study has identified significant differences in the group of genetic liver diseases compared to the control group. We observed that pregnant women with chronic hepatopathy due to genetic disorders have a higher rate of fetal growth restriction. Although the literature describes associations between these genetic pathologies and increased rates of miscarriages and preeclampsia[53,54], we did not observe these in our study, and this may be due to a limited sample size.

Subgroup analysis

G1a: Pregnant women with liver cirrhosis and portal hypertension vs without liver cirrhosis and portal hypertension

Obstetric outcomes

The results of our study revealed significant disparities between the two subgroups regarding the rates of live births, miscarriages, and pregnancy terminations. In all these evaluated variables, the group of women with liver cirrhosis showed unfavorable obstetric outcomes, consistent with what is described in the literature.[55]

In previous studies[55], there were no significant differences observed between women with liver cirrhosis and those without it, regarding hypertensive disorders, fetal growth restriction, and prematurity rates.

Perinatal outcomes

Regarding perinatal outcomes, a significant difference was observed only in the incidence of complications at birth, with all neonates born to mothers with liver cirrhosis presenting neonatal jaundice as a complication.

Analytical parameters

In our study, no significant differences were observed between the groups regarding the incidence of anemia, thrombocytopenia, and infections. However, it was noted that all cirrhotic women exhibited cholestasis, consistent with prior findings associating cirrhosis with an increased risk of developing intrahepatic cholestasis during pregnancy.[23] This cholestasis in the context arises from the interaction between cirrhosis, compromising liver function and bile acid metabolism due to advanced liver fibrosis, and the hormonal changes of pregnancy, creating an environment conducive to the development of intrahepatic cholestasis in women with this chronic liver disease.

Marschall et al.[56] mention an association between the diagnosis of intrahepatic cholestasis of pregnancy and an increased risk of developing hepatobiliary diseases later on, with a yearly increment of 1%. Additionally, the prior presence of liver disease also increases the chances of subsequent ICP diagnosis. This positive association between ICP and other hepatobiliary diseases is independent of temporality and may be attributed, in part, to shared risk factors, such as variants in the ABCB4 gene. Notably, this mutation was present in all patients in our study with progressive familial intrahepatic cholestasis (PFIC). Although that study primarily focused on the relationship between the presence of hepatitis C and the development of ICP, the explanations provided regarding the disruption of bile acid homeostasis and the interaction of hepatic inflammatory processes with physiological changes during pregnancy suggest a disturbance in bile flow and exacerbation of cholestasis that may also apply to other chronic liver diseases.

Flares during pregnancy and in the postpartum period

During the postpartum period, there were no significant differences observed between the two subgroups, concerning the occurrence of flares. However, the rate of flares during pregnancy was higher in pregnant women with cirrhotic pathology, and all cirrhotic pregnant women experienced decompensation of their underlying disease. In the literature, the most commonly described decompensation in pregnant women with cirrhosis is esophageal variceal bleeding, with rates of approximately 33% and up to 50% in women with portal hypertension.[5] In our sample, the two pregnant women who experienced this complication resulted in miscarriage and pregnancy termination. The remaining cirrhotic pregnant women carried their pregnancies to term, although all experienced worsening of their liver function parameters, consistent with what is described in the literature.

While the literature describes flare rates during pregnancy in women with autoimmune pathology ranging from 7,00–33,00%[4], our study observed a percentage of 42,11% of flares in these pregnant women. However, all flares were mild, and there was no requirement for pregnancy termination. These findings within our cohort may be attributed to the limited number of patients exhibiting such pathologies in our sample.

A wide range of graft rejection prevalence has been reported in many studies, ranging from 0 to 17,00%. [28] In our study, patients were not diagnosed with acute rejection episodes during pregnancy, although an increase in liver enzymes was observed both during pregnancy and in the postpartum period.

The present study has certain limitations that warrant consideration. Firstly, the analysis was conducted on a per-pregnancy basis, without accounting for the possibility of multiple pregnancies within the same patient, which may introduce a bias in the results. Additionally, the sample size was relatively small, consisting of only 59 patients with chronic liver disorders and 84 pregnancies over 17 years, reflecting the rarity of the condition. Consequently, conducting multicenter studies may be necessary to expand the sample size and improve generalizability. Lastly, it is important to note that the retrospective design of this study may have led to missing data and clinical biases, representing a major limitation. For those reasons and considering the results from this retrospective study, it would be interesting to perform a prospective study, that would lessen the follow-up losses and deliver higher accuracy results.

Conclusion

Our study demonstrated that women with chronic liver disorders are associated with a significantly increased risk of pregnancy complications. Among the various chronic pathologies analyzed, cirrhotic patients were the group that correlated with the highest obstetric and perinatal risks, followed by pregnant women with autoimmune pathology and those with liver transplants. Within these complications, we observed that fetal growth restriction, gestational age at birth, birth weight, and the need for admission to neonatal intensive care units were the most frequent. However, with close and multidisciplinary monitoring of these patients, the neonatal survival rate can be similar to that of the general population, emphasizing the importance of monitoring pregnant women with liver disorders during pregnancy.

Tables

Table I - Characterization of the study sample group (CLD)

Variable	Study group
Number of pregnancies, n	84
CLD etiology	
Liver transplantation, n (%)	38 (45,24)
PAF	21 (55,26)
Autoimmune diseases	8 (21,05)
Wilson´s disease	4 (10,53)
Hepatic toxicity	3 (7,89)
Others	2 (5,26)
Autoimmune diseases, n (%)	21 (25,00)
Autoimmune hepatitis	18 (75,00)
Overlap syndrome	2 (8,33)
Primary biliary cholangitis	1 (4,76)
Genetic diseases, n (%)	18 (21,43)
Alpha-1-antitrypsin defiency	13 (72,22)
Progressive familial intrahepatic cholestasis	3 (16,67)
Wilson´s disease	1 (5,56)
VLCAD deficiency	1 (5,56)
Liver cirrhosis and portal hypertension, n (%)	7 (8,33)

CLD – Chronic Liver Disorder; PAF - Familial Amyloid Polyneuropathy; VLCAD - Very Long-Chain Acyl-CoA Dehydrogenase

Values are expressed as n-number of cases (percentage); p values of less than 0,05 were considered statistically significant; the total denominator (N) in each variable might differ according to the missings

Table II - Obstetric History

Variable	Study Group	Control Group	*p* value
Primiparous, n (%)	37 (44,58)	64 (38,10)	0,290
Multiparous, n (%)	46 (55,42)	104 (61,90)	0,320
APO, n (%)	41 (64,06)	28 (16,67)	**<0,001**
▪ Liver cirrhosis and portal hypertension	5 (71,43)	28 (16,67)	**<0,001**
▪ Autoimmune diseases	14 (50,00)	28 (16,67)	**<0,001**
▪ Liver transplantation	16 (42,11)	28 (16,67)	**<0,001**
▪ Genetic diseases	6 (33,33)	28 (16,67)	0,080
Pregnancies with flares (during preg.), n (%)	23 (29,87)	-	-
▪ Liver cirrhosis and portal hypertension	3 (100)	-	-
▪ Autoimmune diseases	8 (42,11)	-	-
▪ Liver transplantation	6 (16,22)	-	-
▪ Genetic diseases	6 (33,33)	-	-
Flares during pregnancy, n (%)	29 (72,50)	-	-
▪ 1st trimester	2 (6,90)	-	-
▪ 2nd trimester	7 (24,14)	-	-
▪ 3rd trimester	20 (68,97)	-	-
Pregnancies with flares (postpartum), n (%)	11 (15,94)	-	-
▪ Liver cirrhosis and portal hypertension	1 (33,33)	-	-
▪ Autoimmune diseases	4 (21,05)	-	-
▪ Liver transplantation	6 (20,69)	-	-
▪ Genetic diseases	0	-	-

APO- Adverse Pregnancy Outcomes; Preg. – Pregnancy

Values are expressed as n-number of cases (percentage); p values of less than 0,05 were considered statistically significant; the total denominator (N) in each variable might differ according to the missings

Table III - Diagnosis ages and time intervals until pregnancy

Variable	Study group	Control group	*p* value
Maternal age at conception (years), mean (sd)	32,42 (±5,87)	31,69 (±5,50)	0,167
Age at CLD diagnosis (years), mean (sd)	22,89 (±9,29)	-	-
Duration of disease before pregnancy (years), mean (sd)	9,04 (±6,89)	-	-
Time interval between liver transplantation and pregnancy (years), mean (sd)	6,53 (±4,76)	-	-

CLD – Chronic Liver Disorder

Values are expressed as mean (sd-standard deviation); p values of less than 0,05 were considered statistically significant; the total denominator (N) in each variable might differ according to the missings

Table IV – Medication during preconception

Medication during the periconception period	Study group	Control group	*p* value
n	84	168	
Medication, n (%)	63 (77, 78)	-	-
Tacrolimus, n (%)	28 (34,57)	-	-
Prednisolone, n (%)	19 (23,46)	-	-
Azathioprine, n (%)	15 (18,52)	-	-
Ciclosporine, n (%)	13 (16,05)	-	-
UDCA, n (%)	4 (4,94)	-	-
Cholestyramine, n (%)	3 (3,70)	-	-
Hydroxychloroquin, n (%)	3 (3,70)	-	-
MMF, n (%)	1 (1,23)	-	-

UDCA - Ursodeoxycholic acid; MMF - Mycophenolate mofetil

Values are expressed as n-number of cases (percentage); p values of less than 0,05 were considered statistically significant; the total denominator (N) in each variable might differ according to the missings

Table V – Medication during pregnancy

Variable	Study group	Control group	*p* value
Specific medication during pregnancy			
Aspirin, n (%)	59 (70,23)	17 (10,12)	**<0,001**
LMWH, n (%)	20 (23,80)	4 (2,38)	**<0,001**
Increased dose, n (%)	16 (23,53)	-	-
New medication, n (%)	23 (34,33)	-	-

LMWH - Low Molecular Weight Heparin

Values are expressed as n-number of cases (percentage); p values of less than 0,05 were considered statistically significant; the total denominator (N) in each variable might differ according to the missings

Table VI - Obstetric Outcomes

Variable	Study group	Control group	*p* value
Pregnancy complications			
Gestational Hypertension, n (%)	1 (1,45)	6 (3,57)	0,381
▪ Liver cirrhosis and portal hypertension	0	6 (3,57)	-
▪ Autoimmune diseases	0	6 (3,57)	-
▪ Liver transplantation	1 (3,45)	6 (3,57)	0,974
▪ Genetic diseases	0	6 (3,57)	-
Gestational Diabetes, n (%)	4 (5,71)	12 (7,14)	0,688
▪ Liver cirrhosis and portal hypertension	0	12 (7,14)	-
▪ Autoimmune diseases	2 (11,11)	12 (7,14)	0,544
▪ Liver transplantation	1 (3,23)	12 (7,14)	0,417
▪ Genetic diseases	1 (5,56)	12 (7,14)	0,802
Preeclampsia, n (%)	1 (1,41)	5 (2,98)	0,479
▪ Liver cirrhosis and portal hypertension	0	5 (2,98)	-
▪ Autoimmune diseases	0	5 (2,98)	-
▪ Liver transplantation	1 (3,23)	5 (2,98)	0,940
▪ Genetic diseases	0	5 (2,98)	-
FGR, n (%)	16 (22,53)	9 (5,36)	**<0,001**
▪ Liver cirrhosis and portal hypertension	1 (33,33)	9 (5,36)	**0,041**
▪ Autoimmune diseases	5 (26,32)	9 (5,36)	**0,001**
▪ Liver transplantation	4 (12,90)	9 (5,36)	0,118
▪ Genetic diseases	6 (33,34)	9 (5,36)	**<0,001**
Live birth, n (%)	70 (83,33)	168 (100,00)	**<0,001**
▪ Liver cirrhosis and portal hypertension	3 (42,86)	168 (100,00)	**<0,001**
▪ Autoimmune diseases	19 (90,48)	168 (100,00)	**<0,001**
▪ Liver transplantation	30 (78,95)	168 (100,00)	**<0,001**
▪ Genetic diseases	18 (100,00)	168 (100,00)	**-**
Miscarriage, n (%)	7 (8,54)	0 (0)	-
▪ Liver cirrhosis and portal hypertension	2 (28,57)	0 (0)	-
▪ Autoimmune diseases	2 (9,52)	0 (0)	-
▪ Liver transplantation	3 (7,89)	0 (0)	-
▪ Genetic diseases	0	0 (0)	-
Termination of pregnancy, n (%)	7 (8,54)	0 (0)	-
▪ Liver cirrhosis and portal hypertension	2 (28,57)	0 (0)	-
▪ Autoimmune diseases	0	0 (0)	-
▪ Liver transplantation	5 (14,29)	0 (0)	-
▪ Genetic diseases	0	0 (0)	-
Preterm Delivery, n (%)	15 (21,43)	21 (12,50)	0,080
▪ Liver cirrhosis and portal hypertension	0	21 (12,50)	-
▪ Autoimmune diseases	9 (47,37)	21 (12,50)	**<0,001**

▪ Liver transplantation	5 (16,67)	21 (12,50)	0,534
▪ Genetic diseases	1 (5,56)	21 (12,50)	0,386
Gestational age at delivery (weeks), Mean (sd)	36,82 (±2,60)	38,14 (±2,03)	**<0,001**
▪ Liver cirrhosis and portal hypertension	37,00 (±0,00)	38,14 (±2,03)	0,166
▪ Autoimmune diseases	35,68 (±3,37)	38,14 (±2,03)	**0,003**
▪ Liver transplantation	37,14 (±2,24)	38,14 (±2,03)	**0,009**
▪ Genetic diseases	37,50 (±2,15)	38,14 (±2,03)	0,103
Cesarean Section, n (%)	27 (39,71)	64 (38,09)	0,818
▪ Liver cirrhosis and portal hypertension	2 (66,67)	64 (38,09)	0,314
▪ Autoimmune diseases	11 (57,89)	64 (38,09)	0,095
▪ Liver transplantation	11 (39,29)	64 (38,09)	0,904
▪ Genetic diseases	3 (16,67)	64 (38,09)	0,072

FGR - Fetal growth restriction

Values are expressed as mean (sd-standard deviation) or n-number of cases (percentage); p values of less than 0,05 were considered statistically significant; the total denominator (N) in each variable might differ according to the missings

Table VII – Perinatal Outcomes

Variable	Study group	Control group	*p* value
Apgar score at 5 minutes, mean (sd)	9,52 (±0,70)	9,71 (±0,66)	**0,037**
▪ Liver cirrhosis and portal hypertension	9,33 (±1,16)	9,71 (±0,66)	0,168
▪ Autoimmune diseases	9,31 (±0,87)	9,71 (±0,66)	**0,014**
▪ Liver transplantation	9,65 (±0,75)	9,71 (±0,66)	0,350
▪ Genetic diseases	9,56 (±0,71)	9,71 (±0,66)	0,177
Birth weight (g), mean (sd)	2754,38 (±528,24)	3031,52 (±523,17)	**<0,001**
▪ Liver cirrhosis and portal hypertension	2686,67 (±420,99)	3031,52 (±523,17)	0,129
▪ Autoimmune diseases	2499,71 (±697,33)	3031,52 (±523,17)	**<0,001**
▪ Liver transplantation	2825,00 (±546,21)	3031,52 (±523,17)	**0,032**
▪ Genetic diseases	2904,17 (±491,95)	3031,52 (±523,17)	0,163
Need for ICU admission, n (%)	10 (15,62)	11 (6,58)	**0,031**
▪ Liver cirrhosis and portal hypertension	0	11 (6,58)	-
▪ Autoimmune diseases	7 (46,67)	11 (6,58)	**<0,001**
▪ Liver transplantation	2 (6,90)	11 (6,58)	0,944
▪ Genetic diseases	1 (5,56)	11 (6,58)	0,871
Complications at birth, n (%)	17 (28,81)	41 (24,40)	0,396
▪ Liver cirrhosis and portal hypertension	3 (100)	41 (24,40)	**0,003**
▪ Autoimmune diseases	5 (50,00)	41 (24,40)	0,072
▪ Liver transplantation	2 (6,90)	41 (24,40)	**0,035**
▪ Genetic diseases	8 (44,44)	41 (24,40)	0,067
Fetal malformations, n (%)	3 (5,08)	11 (6,54)	0,688
▪ Liver cirrhosis and portal hypertension	0	11 (6,54)	-
▪ Autoimmune diseases	2 (6,67)	11 (6,54)	0,191
▪ Liver transplantation	1 (3,70)	11 (6,54)	0,568
▪ Genetic diseases	0	11 (6,54)	-

ICU- Intensive Care Unit

Values are expressed as mean (sd-standard deviation) or n-number of cases (percentage); p values of less than 0,05 were considered statistically significant; the total denominator (N) in each variable might differ according to the missings

Table VIII – Comparison maternal age at conception between non-cirrhosis and cirrhosis group

Variable	Non-cirrhosis group	Cirrhosis group	*p* value
Maternal age at conception (years), mean (sd)	32,30 (±6,00)	33,71 (±4,11)	0,272

Values are expressed as mean (sd-standard deviation); p values of less than 0,05 were considered statistically significant; the total denominator (N) in each variable might differ according to the missings

Table IX– Comparison obstetric outcomes between non-cirrhosis and cirrhosis group

Variable	Non-cirrhosis group	Cirrhosis group	*p* value
Pregnancy complications			
Gestational Hypertension, n (%)	1 (1,52)	0 (0)	-
Gestational Diabetes, n (%)	4 (5,97)	0 (0)	-
Preeclampsia, n (%)	1 (1,47)	0 (0)	-
FGR, n (%)	14 (20,89)	1 (33,33)	0,607
Live birth, n (%)	67 (87,01)	3 (42,86)	**0,003**
Miscarriage, n (%)	5 (6,66)	2 (28,57)	**0,047**
Termination of pregnancy, n (%)	5 (6,66)	2 (28,57)	**0,047**
Preterm Delivery, n (%)	15 (22,38)	0 (0)	**-**
Gestational age at delivery (weeks), mean (sd)	36,82 (±2,66)	37,00 (±100)	0,453
Cesarean Section, n (%)	25 (38,46)	2 (66,66)	0,329

FGR - Fetal growth restriction

Values are expressed as mean (sd-standard deviation) or n-number of cases (percentage); p values of less than 0,05 were considered statistically significant; the total denominator (N) in each variable might differ according to the missings

Table X – Comparison perinatal outcomes between non-cirrhosis and cirrhosis group

Variable	Non-cirrhosis group	Cirrhosis group	*p* value
Apgar Score at 5 minutes, mean (sd)	9,53 (±0,77)	9,33 (±1,16)	0,334
Birth weight (g), mean (sd)	2751,70(±591,45)	2686,67(±420,99)	0,419
Need for ICU admission, n (%)	10 (16,13)	0 (0)	-
Complications at birth, n (%)	15 (26,31)	3 (100)	**0,007**
Fetal malformations, n (%)	3 (5,26)	0 (0)	-

ICU- Intensive Care Unit

Values are expressed as mean (sd-standard deviation) or n-number of cases (percentage); p values of less than 0,05 were considered statistically significant; the total denominator (N) in each variable might differ according to the missings

Table XI - Comparison analytical parameters and flares during pregnancy and postpartum outcomes between non-cirrhosis and cirrhosis group

Variable	Non-cirrhosis group	Cirrhosis group	*p* value
Anemia, n (%)	21 (27,63)	1 (14,28)	0,444
Thrombocytopenia, n (%)	6 (7,79)	1 (14,28)	0,552
Infection, n (%)	11 (14,47)	0 (0)	-
Cholestasis, n (%)	14 (18,66)	3 (100)	**<0,001**
Pregnancies with flares (during preg.), n (%)	20 (27,03)	3 (100)	**0,007**
Pregnancies with flares (postpartum), n (%)	10 (15,15)	1 (33,33)	0,400

Preg. - Pregnancy

Values are expressed as n-number of cases (percentage); p values of less than 0,05 were considered statistically significant; the total denominator (N) in each variable might differ according to the missings

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