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Clinical and obstetrical management of pregnant women with autoimmune hepatitis complicated by moderate or severe thrombocytopenia☆

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ABSTRACT

Objective: To describe the management of prenatal care and delivery in patients bearing autoimmune hepatitis associated with moderate or severe thrombocytopenia.
Methods: This study was performed in a tertiary level university hospital. Thiteen pregnancies in ten patients diagnosed with autoimmune hepatitis, complicated by thrombocytopenia, were retrospectively analyzed. The inclusion criteria were as follows: clinical diagnosis of autoimmune hepatitis, moderate or severe thrombocytopenia (platelet count $<100 \times 10^3/mm^3$), gestational age at birth over 22 weeks, and patient followed-up by a specialized team at the institution. The variables studied were: maternal age, parity, treatment regimen, platelet count, examinations for investigation of hepatic function, type of delivery, weight at birth, and gestational age at the time of delivery.
Results: The average maternal age was 24.5 years (SD = 5.3) and six (50%) occurred in nulliparous women. During pregnancy, monotherapy with prednisone was adopted in 11 cases (92%). According to the autoantibody profiles, seven pregnancies (58%) had the autoimmune hepatitis type I diagnosis, two pregnancies had type II (17%), and three pregnancies (25%) had cryptogenic chronic hepatitis (undetectable titers of autoantibodies). Portal hypertension was featured in 11 pregnancies (92%). The average gestational age at delivery was 36.9 weeks (SD = 1.5 weeks), with an average weight at birth of 2,446g (SD = 655g). Eight infants (67%) were small for gestational age. At the time of delivery, severe thrombocytopenia was featured in four cases (33%) and cesarean surgery was performed in seven cases (58%). Complications at delivery occurred in three cases (25%), one patient presented uterine atony, and two patients presented perineal bruising. There was no perinatal or maternal death.

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Conclusion: The complications of thrombocytopenic patients with autoimmune hepatitis are elevated; nevertheless, with appropriate attention and care, they can be resolved. The association between two severe pathologies appears to increase the risk of prematurity and fetal growth restriction, demanding specialized prenatal care, as well as surveillance of fetal well-being.

Manejo clínico e obstétrico em gestantes portadoras de hepatite autoimune complicada pela plaquetopenia moderada ou grave

R E S U M O

Objetivo: O presente trabalho tem como objetivo descrever o manejo do pré-natal e do parto em pacientes portadoras de hepatite autoimune associada à plaquetopenia moderada ou grave.
Métodos: Este trabalho foi realizado em hospital universitário, de nível terciário. Foram analisadas, retrospectivamente, 13 gestações em dez pacientes com diagnóstico de hepatite autoimune complicadas pela plaquetopenia. Os critérios de inclusão foram: diagnóstico clínico de hepatite autoimune, plaquetopenia moderada ou grave (contagem de plaquetas < 100 x 10^3/mm^3), idade gestacional ao nascimento acima de 22 semanas e pacientes acompanhadas por equipe especializada da instituição. As variáveis estudadas incluíram idade materna, paridade, os regimes de tratamento, contagem de plaquetas, exames para investigação da função hepática, tipo de parto, peso ao nascer e idade gestacional no momento do parto.
Resultados: A média da idade materna foi de 24,5 anos (DP = 5,3) e seis (50%) ocorreram em nulíparas. Durante a gravidez, a monoterapia com prednisona foi adotada em 11 (92%) casos. De acordo com o perfil de autoanticorpos, sete (58%) gestações possuíam diagnóstico de hepatite autoimune tipo I, duas (17%) do tipo II e três (25%) eram portadoras de hepatite crônica criptogênica (títulos de autoanticorpos indetectáveis). A hipertensão portal foi caracterizada em 11 (92%) gestações. A idade gestacional média no parto foi de 36,9 semanas (DP = 1,5 semana), com média de peso ao nascer de 2446g (DP = 655g), sendo oito (67%) pequenos para a idade gestacional. No momento do parto, a plaquetopenia grave foi caracterizada em quatro (33%) casos e a cesárea foi realizada em sete (58%). As complicações no parto ocorreram em três casos (25%), uma paciente apresentou atonia uterina e duas, hematoma perineal. Não houve morte materna ou perinatal.
Conclusão: As complicações em pacientes plaquetopênicas com hepatite autoimune são elevadas, no entanto, com os cuidados e atenção necessários, podem ser contornáveis. A associação de duas patologias graves parece aumentar o risco de prematuridade e restrição do crescimento fetal, demandando atenção pré-natal especializada, bem como vigilância do bem-estar do concepto.

Palavras-chave:
Hepatite autoimune
Gestação
Trombocitopenia
Cuidado pré-natal

Introduction

Autoimmune hepatitis is a chronic inflammatory disease that is prevalent in young women, affecting the hepatic parenchyma by means of autoantibodies. It presents a variable clinical picture from asymptomatic to acute liver failure. In a general way, it is characterized by non-specific symptoms such as: fatigue, faintness, and discomfort, followed by an increase in hepatic enzymes. There is usually an association with other autoimmune diseases, and a genetic predisposition has been described. In spite of its severity, it presents a good response to corticosteroid clinical treatment.[1]

As autoimmune hepatitis treatment strategies improved, pregnancy in such patients increased, especially in patients with the disease under control.[2] Notwithstanding, few studies investigate the results and consequences that the disease and its treatment can have on to pregnancy, and the implications at the time of delivery.

The present study aims to describe the management of prenatal care and delivery in patients bearing autoimmune hepatitis associated with moderate or severe thrombocytopenia. Such an investigation is justified since few studies have specifically approached this subgroup presenting a higher severity. In addition, laboratory evolution, frequency of bleeding complications, and the healthcare needed in pregnancy, delivery, and puerperium were also evaluated.

Methods

This study was performed in a tertiary level university hospital and covered the period from April, 2001 to July, 2011. It was a retrospective and descriptive study, in which data were collected from medical records of pregnant women diagnosed with autoimmune hepatitis and moderate or sever thrombocytopenia. These patients were followed-up by the prenatal team specialized in hemopathies and pregnancy

at this institution. The research was approved by the ethics committee in research of this institution (project No. 695/08).

Pregnant women were followed-up from prenatal care until the final phase of pregnancy, at the delivery, and puerperium. The following inclusion criteria were adopted: autoimmune hepatitis diagnosis established previously to pregnancy by the presence of auto-antibodies and/or hepatic alterations compatible with the disease; presence of moderate thrombocytopenia (between 50 and $100x10^3$ platelets/mm^3) or severe thrombocytopenia (< $50x10^3$ platelets/mm^3) during the pregnancy; start of prenatal care at least in the second gestational trimester; and follow-up until delivery and puerperium.

The determination of the type of autoimmune hepatitis was performed based on autoantibodies profile. Patients bearing titers of antinuclear antibodies (ANA autoantibodies) anti-smooth muscle (ASM) equal to or greater than 1/40 were classified as type I; these same titers for ALKM-1antibody (kidney and liver microsomal) and ALC-1 (hepatic cytosol) characterized autoimmune hepatitis type II.[3] When the titers of auto-antibodies were undetectable, cryptogenic chronic hepatitis was characterized.

Prenatal care of those patients was initially performed by monthly consultations, until the end of the second trimester, at which point they became fortnightly; when closer to the end of pregnancy, the consultations were performed on a weekly basis. At the start of prenatal care, besides the usual laboratory tests, examinations for investigating hepatic function were requested: alanine transaminase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (AP), direct billirubin (DB), and indirect billirubin (IB). The adopted medication was based on the treatment in use at the moment in which the pregnancy occurred, generally prednisone corticotherapy. Clinical or obstetrical complications verified during the pregnancy were studied. Hepatic function examinations, platelet count, and hemoglobin (Hb) and haematocrit (Ht) levels were serially monitored according to the case severity, at prenatal care returns, and as needed by alteration of these factors, with earlier returns. A coagulogram (activated partial thromboplastin time – APTT, prothrombin time – PT, and thrombin time – TT) was performed in the third trimester and close to the date of delivery. Besides specific autoantibodies profile data, the results of hepatic biopsy and/or clinical history of portal hypertension and esophageal varices were surveyed. During prenatal follow-up, the presence of esophageal varices was reviewed through high digestive endoscopy, mainly for verifying varicose vein caliber and choosing the method of delivery.

Fetal follow-up during the prenatal care in autoimmune hepatitis cases was performed through obstetrical ultrasonography for estimating fetal weight and weekly vitality exams (tocodynamometry, fetal biophysical profile, and amniotic fluid index [AFI]) from the 32nd week of pregnancy, which allowed the diagnostic suspicion of fetal growth (fetal estimated weight < 10th percentile) and changes in the amniotic liquid volume (oligohydramnios was characterized when the AFI was lower than or equal to 5.0 cm). Delivery (vaginal or cesarean) was scheduled, respecting the conventional obstetrical conditions for indicating cesarean surgery, such as Iterative cesarean, breech deliveries, meconium, impossibility of labor induction by presence of previous cesarean surgery, and changes derived from the base disease found at the prenatal follow-up, such as large caliber esophageal varices. Labor induction was performed by intravenous infusion of oxytocin, when there were contraindications to its use. When the cervix was unfavorable (Bishop's score lower than five), cervix preparation was performed by using misoprostol and later induced with oxytocin. Fetal and uterine contraction monitoring by cardiotocography was performed during the period of delivery. At childbirth, when the pudendum nerve blockade was indicated by vaginal delivery, 2% lidocaine was used. The following variable factors concerning perinatal results were investigated: gestational age at childbirth; occurrence of fetal suffering; weight at birth; newborn weight adequacy; Apgar scores at the 1st, 5th, and 10th minute; and perinatal mortality.

Table 1 – Maternal features, and clinical and obstetrical data from pregnant women with autoimmune hepatitis complicated by moderate or severe thrombocytopenia (n = 12).

Feature	Value
Maternal age, years, average (SD)	24.5 (5.3)
Nulliparous, n (%)	6 (50%)
Types of autoimmune hepatitis, n (%)	
Type 1	7 (58%)
Type 2	2 (17%)
Cryptogenic chronic hepatitis	3 (25%)
Esophageal varices, n (%)	
Fine caliber or eradicated	7 (58%)
Medium/large caliber	5 (42%)
Gestational age at childbirth, weeks, average (SD)	36.9 (1.5)
Type of delivery, n (%)	
Vaginal	5 (42%)
Cesarean	7 (58%)
Delivery complications	
Perineal hematoma	2 (17%)
Uterine atony	1 (8%)
Weight at birth, g, average (SD)	2446 (655)
Weight at birth adequacy, n (%)	
AGA	3 (25%)
SGA	8 (67%)
LGAG	1 (8%)
Apgar score at 1st min < 7, n (%)	1 (8%)
Apgar score at 5th min < 7, n (%)	0

AGA, adequate for gestational age; SGA, small for gestational age; LGA, large for gestational age; SD, standard deviation.

Table 2 – Description of pregnancies in patients bearing autoimmune hepatitis, complicated by moderate or severe thrombocytopenia (n = 12).

Case	Profile of antibodies	Gestation	Age (years)	Obstetrical complication	Treatment (predinisone)	Cirrose hepática	Esophageal varices	Platelets at delivery[a] (thousand/ mm^3)	Gestational age at delivery (weeks)	Type of delivery	Weight at birth (g)	Postpartum complication
1	SMA (kidney) vascular 1/160 glomerular 1/80 tubular + and SMA (stomach) 1/160	1	20	Urinary infection	60 mg/d	+	Fine	48	37.4	Vaginal	2,570	Uterine atony
		2	26	Premature rupture of membranes + gestational diabetes	20 mg/d	+	Fine	111	37.6	Vaginal	2,970	-
2	–	1	19	Fetal growth restriction	5 mg/d	-	Absent	78	37.6	Cesarean	2,410	-
3	SMA (kidney) vascular + glomerular + tubular and SMA (stomach) 1/40	1	16	-	7,5 mg/d	+	Fine	88	37.9	Forceps	2,470	-
4	ALKM -1 (kidney) > 1/320 and ALKM-1 (stomach) > 1/320	1	24	-	20 mg/d	-	Average	47	38.4	Cesarean	4,120	-
5	SMA (kidney) vascular 1/40 glomerular -tubular - and SMA (stomach) 1/40	1	33	-	No	+	Large	77	38	Cesarean	2,500	-
6	SMA (kidney) vascular > 1/320 glomerular 1/320 tubular + and SMA (stomach) >1/320	1	23	Premature rupture of membranes + Premature labor and delivery	20 mg/d	+	Fine	49	35	Cesarean	2,510	-
7	SMA (kidney) vascular > 1/320 glomerular - tubular - and SMA (stomach) > 1/320	1	28	Severe fetal growth restriction	20 mg/d	-	Average	22	36.9	Forceps	1,910	Perineal hematoma
8	Negative antibodies	1	25	-	20 mg/d	+	Eradicated	55	38	Vaginal	2,440	Perineal hematoma
9	Negative antibodies	1	30	Fetal growth restriction + reduction of AF	20 mg/d	-	Average	51	33.4	Cesarean	1,580	-
		2	31	Fetal growth restriction + oligohydramnios	20 mg/d	-	Average	98	36.6	Cesarean	2,110	-
10	ALC-1 1/160	1	20	Pre-eclampsia	7,5 mg/d	-	Eradicated	80	35.7	Cesarean	1,760	-

SMA, anti-smooth muscle antibody, vascular, glomerular and tubular - kidney and liver; ALKM-1, antimicrosomal antibody, liver and kidney; ALC-1, anti-liver citosol antibody; AF, amniotic fluid.
[a]Platelet count at delivery before receiving platelet aphaeresis as needed.

Table 3 – Gestation laboratory profile in patients with autoimmune hepatitis complicated by moderate or severe thrombocytopenia (n = 12).

	Pre-gestational (n = 10)	1st trimester 2nd trimester (n = 11)	3rd trimester (n = 12)	Delivery (n = 12)	Puerperium (n = 11)
Hemoglobin (g/dL)	13.05 (10.9-15.1)	11.5 (10.6-14.1)	12.35 (11.3-15.1)	11.45 (7.4-13.4)	12.1 (8.2-15.3)
Haematocrit (g/dL)	38.5 (31.8-44.5)	34.2 (31.4-41.4)	35.7 (32.7-45.8)	33.95 (23.4-40.8)	36.8 (28.2-45.1)
Platelets (n/mm^3)	79.5 (44-97)	58 (29-101)	59 (31-97)	66 (22-111)	62 (43-106)
AST (U/L)	24.5 (16-56)	22 (16-44)	20.5 (13-45)	24 (13-94)	33 (25-67)
ALT (U/L)	22 (15-79)	17 (11-38)	15 (11-33)	16 (7-44)	24 (14-205)
GGT (U/L)	51.5 (22-208)	38 (15-192)	23 (11-124)	87 (11-181)	71 (23-291)
FA (U/L)	69.5 (24-123)	51 (29-145)	76.5 (33-138)	105 (49-195)	92 (67-265)

Data expressed as median (minimum – maximum). AST, aspartate aminotransferase; ALT, alanine transaminase; GGT, gamma-glutamyltransferase; AF, alkaline phophatase.

Gestational age was calculated from the date of the last menstrual period (DLM), when it was compatible with the gestational age estimated by the ultrasonography, performed up to the 20th week of gestation. In cases in which agreement was not observed, the gestational age was calculated through data of the first ultrasonography. The weight at birth in grams, weighed at the delivery room, was compared to the normality curve by Alexander et al.,[4] and the results were classified as follows: small for the gestational age, weight at birth lower than the 10th percentile of the corresponding rank; adequate, between the 10th and 90th percentile; and large, above the 90th percentile.

Medcalc (v. 11.5.1.0) was used for analyzing the results. The categorical variables were descriptively analyzed by calculating relative and absolute frequencies. For analyzing continuous variables, the results were expressed as averages, medians, standard deviations, minimum values, and maximum values.

Results

The present study followed up 13 pregnancies in ten patients with autoimmune hepatitis. One case evolved to miscarriage in the first trimester, diagnosed with anembryonic gestation, and was not included in the analysis. Maternal features and clinical data of the pregnant women with autoimmune hepatitis and thrombocytopenia who reached the third trimester are described on Table 1.

Half of the cases occurred in nulliparous patients. According to the autoantibodies profile, seven gestations (58%) had type I autoimmune hepatitis, two gestations (17%) had type II, and three gestations (25%) had cryptogenic chronic hepatitis (titers of undetectable auto-antibodies). Portal hypertension was characterized in 11 gestations (92%) by the presence of esophageal varices in pregnancy (which in some instances had been eradicated) detected by high digestive endoscopy.

In six pregnancies (50%), thrombocytopenia was characterized as severe in some moment of pregnancy. Regarding the serological profile in prenatal care, all pregnant women had negative serology to human immunodeficiency virus (HIV), syphilis, and hepatitis B and C. No gestation presented infection by toxoplasmosis or rubella.

The description of cases with the antibodies profile and obstetrical complications is presented on Table 2. Five patients had hepatic biopsy previous to pregnancy, and all of them had confirmed cirrhosis, in different degrees of activity. The clinical treatment adopted in pregnancy was prednisone in 11 cases (92%), for controlling the base disease. In patients using azathioprine, the medication was stopped in the first trimester, when pregnancy was diagnosed. At the time of delivery, severe thrombocytopenia was featured in four cases (33%), and complications in childbirth occurred in three cases (25%). The proportion of newborn infants small for the gestational age was 67%; there was no maternal or neonatal mortality.

Table 3 shows the laboratory follow-up evolution of the main parameters in pre-gestational, gestational, and post-childbirth periods. A reduction of red blood cell parameters during the pregnancy was observed, followed by a return to pre-gestation levels in the postpartum period.

Discussion

Autoimmune hepatitis is associated with reduction of women's fertility; however, the adequate control of disease increases the number of pregnancies in women bearing such disorder.[5] Some studies point to the greater risk for fetal loss in these patients, mainly before the 20th gestational week. Schramm et al. reported 14.3% miscarriage in their study with 42 gestations, and Heneghan et al. reported 24% miscarriage in 35 gestations.[6,7] In the largest review of cases on this topic, Candia et al. reported termination of pregnancy in 19% of 101 gestations, besides a perinatal mortality rate of 4%.[8] In the present study, only one gestation evolved to such outcome in the first gestational trimester. However, the present study mainly focused on analyzing the management of pre-natal follow-up and of delivery in cases complicated by thrombocytopenia.

In spite of the common association with other autoimmune disorders (celiac disease, ulcerative rectocolitis, and thyroid diseases),[9] in the present study, no patient presented clinical or laboratory manifestation of this type of pathology.

According to the autoantibodies profile, autoimmune hepatitis can be divided into two main groups, type I and type II. Gleeson et al. stated that type I corresponds to 75% of cases in the general population and that, in some centers, there is a prevalence of 10% to 25% of patients with titers of undetectable or very low autoantibodies. In the present study, three cases were of this category, known as cryptogenic chronic hepatitis.[4]

Terrabuio et al. demonstrated the safety of using prednisone and other immunosuppressants, such as azathioprine, for controlling autoimmune hepatitis in gestation.[10] The modifications pregnancy causes in the disease are not well-known. Autoimmune hepatitis frequently tends to be less aggressive during the pregnancy.[11] There are, however, reports on acute exacerbation with acute hepatic failure during the gestational period.[1] Werner et al. report exacerbation in 10.5% of 63 pregnant women bearing autoimmune hepatitis using multiple immunosuppressants prescriptions.[12] In the present study, azathioprine (when used) was stopped in the first gestational trimester, and the prednisone dose was adjusted to better control the disease. Besides, the laboratory dosages of hepatic enzymes presented a tendency of dropping during gestation, and of returning to the basal levels or rising during puerperium. In this study, no cases presented symptoms of acute exacerbation during pregnancy, and the use of prednisone was not responsible for any type of fetal or maternal involvement.

In the present study, cirrhosis was identified in varied degrees of activity on hepatic biopsies previous to gestation. Lohse et al. demonstrated that even though asymptomatic, early autoimmune hepatitis impairs the hepatic architecture in up to 33% of cases.[1] Taking into account that all of pregnant women followed-up in this study presented a definite diagnosis for autoimmune hepatitis, and also considering the presence of portal hypertension in most of cases, it is possible to conclude that hepatic involvement was relevant, and must have concurred with a given degree of splenomegaly and greater platelet retention. These features confer more severity to cases studied regarding platelet count, requiring more attention and planning by the obstetrician regarding the time of delivery. Delivery should be scheduled with a blood and platelet reserve in case of emergency situations. It is recommended to avoid instrumentalised delivery in cases of severe thrombocytopenia. However, obstetrical indications for reducing the expulsive period are frequently prevalent in childbirth assistance. In the case (case 7) in which perineal hematoma was observed, forceps was indicated by prolonged expulsive period in a fetus presenting growth restriction. In the two cases presenting perineal hematoma, it was not necessary to perform a surgical drain, with improvement by local treatment.

Pregnant women with portal hypertension present a risk for bleeding of esophageal varices of around 20% to 45% in the third trimester. As it is quite difficult to predict the occurrence of high digestive hemorrhage during the delivery, some criteria are used for estimating such a possibility. The greater caliber of veins may indicate risk for bleeding. There are, however, some direct parameters, such as vein pressure and the presence of bleeding points; these data are obtained by high digestive endoscopy.[13] In the present study, only information on the caliber of varices was used, and cesarean surgery was indicated for pregnant women with esophageal varices of medium/large caliber. The use of propanolol in a daily dose of 80 mg was also indicated. When the varices were non-existent or thin, and there were no other contraindications, the preferential method of delivery was vaginal. Fevery et al. postulate that in some cases vasoactive drugs, such as propranolol and spironolactone, can be administered for bleeding prophylaxis during the delivery, in the Valsalva maneuver.[14] In the present study, no patient presented a clinical picture of high digestive hemorrhage during gestation or delivery.

The clinical management of a patient during labor and delivery is complex, as bleeding is expected at the time of delivery. In severe thrombocytopenia with a platelet level lower than 50,000/mm^3, neuroaxis block is routinely contraindicated; when a cesarean section is necessary, general anesthesia is usually indicated. Platelet replacement in the intra-operative period, when needed, can be performed by aphaeresis platelet transfusion. In the assistance to vaginal delivery, generally, the indication is for local anesthesia by pudendum nerve block. Moderate or severe thrombocytopenia restrict the use of peridural analgesia. In the present study, cesarean surgery was performed in seven gestations, and general anesthesia was the option in four of those cases (57%); in the five vaginal deliveries (42% of total), pudendum nerve block was used in three cases. The proportion of cesarean surgeries (58%) in the present study was similar to that reported in this service (56.5%) which assists high-risk pregnancies.[15]

As to the complications directly related to childbirth, two cases evolved to perineal hematoma after vaginal delivery, and in both draining procedures were not needed, with resolution by local treatment. This type of complication is expected in thrombocytopenia cases, in management of delivery, and for this reason it is important to perform rigorous homeostasis and perineal review after the procedure. The same approach is recommended for cesarean surgery; however, as it is a large surgical procedure, the replacement of platelets may sometimes be necessary.

Schramm et al. describe premature birth rates from 6% to 17% in patients with autoimmune hepatitis;[6] Westbrook et al., in a recent study covering 81 gestations, describe prematurity rates of 20%.[16] In the present study, there were five cases (42%) in which the childbirth occurred before the 37th week. The high rate of premature gestations can be explained by the associated comorbidities, especially by fetal growth restriction. Even though two thirds of newborn infants presented small size for the gestational age, none presented any type of malformation, despite the severe pathology and the prescribed treatment. In pregnancies with thrombocytopenia, the surveillance of fetal well-being is essential, as well as monitoring of fetus growth during the prenatal care.[17]

The present study has as a limitation the reduced sample size, which is explained by the greater severity of autoimmune

hepatitis complicating the pregnancy. The severity of cases makes it difficult to standardize clinical and surgical conduct, especially in delivery, which is subject to unpredictable complications.

Conclusion

Autoimmune hepatitis associated with severe or moderate thrombocytopenia in pregnancy makes prenatal management and the assistance to delivery difficult. However, the disease tends to be milder during the gestation, which facilitates clinical treatment and in many cases allows for monotherapy. Treatment with prednisone appears to be sufficient for controlling the disease, but immediately after the end of pregnancy, it is relevant to pay careful attention to the clinical and laboratory follow-up for early detection in case of acute exacerbation of the disease. The bleeding complications in thrombocytopenic patients with autoimmune hepatitis are high, but with the appropriate healthcare and attention, they may be controllable. The association of two severe pathologies appears to increase the risk of prematurity and fetal growth restriction, alerting of the need to focus on specialized prenatal care, for better surveillance of fetal well-being.

Conflict of interest

All authors declare to have no conflict of interest.

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