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Case Report

Treating Preeclampsia in the COVID-19 Era: Is Allopurinol Useful as an Adjuvant Therapy? A Case Report and Review of the Literature

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Abstract: Acute respiratory syndrome-related coronavirus 2, or SARS-CoV-2, mainly affects the vulnerable population, especially those with comorbidities, such as pregnant women. SARS-CoV-2 has been found to cause multiple manifestations, one of which is preeclampsia. In preeclampsia, uric acid is excessively produced in the ischemic placenta and is released into circulation by placental reperfusion. Another effect of uric acid is oxidative stress with the production of oxygen free radicals associated with severe preeclampsia and fetal hypoxia. In our case report, we present the situation of a 38-year-old pregnant woman who developed preeclampsia after infection with SARS-CoV-2 with rapid evolution and an increased level of uric acid. We discuss the option of Allopurinol treatment in the third trimester of pregnancy instead of premature birth, with excellent benefits for both the mother and newborn. Additional clinical correlations between antioxidant treatment with Allopurinol and placental findings are needed.

Keywords: allopurinol; preeclampsia; SARS-CoV-2 infection

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1. Introduction

Pregnancy is a special physiological state compared with the non-pregnant population. Normal pregnancy, being characterized by a series of temporary complex events, involves decidualization, placentation, and partum. These chronological transitions are critical to a normal pregnancy, and any alteration in them could have significant effects on the mother and the fetus. The fact that pregnancy causes an increase in oxidative stress is a well-known phenomenon generated by a normal systemic inflammatory response, the result of which is represented by large amounts of circulating reactive oxygen species (ROS), the placenta being the central organ and major source of ROS. All of this being said, an increased level of oxidative stress during pregnancy could lead to potential tissue damage, although this is counterbalanced by increased synthesis of antioxidants [1].

The researchers who demonstrated, for the first time, the failure regarding the remodeling of the spiral arteries at the level of the placental bed of pregnant women with preeclampsia (PE) were Brosens et al. Subsequent studies have associated this pathology with partial failures in terms of trophoblast invasion and preservation of the muscular layer of the spiral arteries, leading to the phenomenon of intermittent placental perfusion, followed by repeated hypoxia or reoxygenation, thus affecting the placenta during pregnancy. STB (syncytiotrophoblast) and CTB (cytotrophoblast) cells abundantly express an important source of O_2^-, namely xanthine oxidase, via the conversion process of xanthine dehydrogenase, a process that has the hypoxia/reoxygenation phenomenon as a strong stimulus. Xanthine oxidase has a fundamental role in the phenomenon of tissue damage generated by free radicals at the placental level, ischemia being the condition that demonstrates that the balance between ROS and antioxidants is disturbed, leading to damage to proteins, lipids, and DNA [1].

Preeclampsia (PE) is defined as hypertension associated with proteinuria. The values of SBP are $\geq$140 mmHg and DBP are $\geq$90 mmHg, and proteinuria values are >300 mg/24 h after the gestational age of 20 weeks of pregnancy, but normal blood pressure values are initially presented. This problem affects 2–8% of the pregnant population. In preeclampsia uric acid is excessively produced in the ischemic placenta and is released into circulation by placental reperfusion. Another effect of uric acid is oxidative stress with the production of oxygen free radicals associated with severe preeclampsia and fetal hypoxia. PE is associated with a hypoxic–ischemic state of the placenta and high level of ROS [2–8]. In PE, through placental ischemia, excess uric acid is produced, which is associated with maternal and fetal complications [9,10]. Under the effect of estrogen, uric acid decreases in pregnancy [9]. The role of uric acid in the severity of PE was described for the first time in 1934, with importance in maternal–fetal prognosis [10]. Its production in increased amounts occurs in the ischemic–hypoxic placenta, returning to circulation through placental reperfusion. In the third trimester, however, it represents a useful tool to diagnose severe PE [3,11,12], being associated with a prognostic role in maternal and fetal complications.

On the other hand, acute respiratory syndrome-related coronavirus 2, or SARS-CoV-2, is a public health issue that mainly affects the vulnerable population [13]. Acute respiratory syndrome-related coronavirus 2, or SARS-CoV-2, mainly affects the vulnerable population, especially those with comorbidities. SARS-CoV-2 has been found to cause multiple manifestations.

At the beginning of the pandemic, data from the literature indicated that SARS-CoV-2 infection affects the outcome of the pregnant population. It leads to acute respiratory distress syndrome (ARDS), disseminated intravascular disease, multiorgan failure, or pneumonia and important obstetric consequences, for example, premature births, intrauterine growth restriction (IUGR), preeclampsia (PE), miscarriage, fetal hypoxia, stillbirth, and maternal and fetal or neonatal deaths [14]. Additionally, an increase in the rate of cesarean sections was reported [15,16]. R.H. Novoas studied the lethality rate among the general population, which was around 3–4%. Pregnant women, being classified as a high-risk population, required intensive care in a proportion of 50%, according to the literature [16].

However, it was later proven that the opposite was the case, as COVID infection affects only those with comorbidities [13,14].

The specific COVID-19 symptoms that are common include coughing, fever, dyspnea, sore throat, tachypnea, chest pain, myalgia, nasal congestion, nausea, and diarrhea. Laboratory tests have revealed leukopenia with lymphopenia, thrombocytopenia, anemia, increased polymerase chain reaction (PCR), altered ferritin, and increased levels of aspartate aminotransferase (AST) and alanine transaminase (ALT). Additionally, the literature data have indicated increased levels of lactate dehydrogenase (LDH), increased cytolysis, and specific chest radiography changes [16]. These changes are not supported by more recent data from the literature on large cohorts [13,14].

Gabrieli et al. described another consequence of SARS-CoV-2 infection: thromboembolic events [17]. In pregnancy, there is an adaptative mechanism of hypercoagulation to prevent hemorrhages. Venous stasis is common and fibrinolytic activity is decreased [17].

According to specialized studies, disseminated intravascular coagulation can occur in pregnancy associated with SARS-CoV-2 infection, and the importance of low-molecular-weight heparin (LMWH) was described [16,18–23].

In our case report, we present the situation of a 38-year-old pregnant woman who developed preeclampsia after infection with SARS-CoV-2 with rapid evolution and an increased level of uric acid who had the option of Allopurinol treatment in the third trimester of pregnancy instead of premature birth.

2. Case Report

A 38-year-old patient presented to our medical service, being pregnant in the third trimester, complaining of fever. The diagnosis at admission was 35/36 weeks primigravida, live fetus, cephalic presentation, intact membranes, placenta previa, uterine malformation, cervical cerclage, and pyrexia. The patient was complaining of decreased fetal movements. SARS-CoV-2 infection is diagnosed by PCR testing. From the patient's medical history, we noted that the pregnancy was obtained after multiple failed attempts through in vitro fertilization and that the patient had a subseptate uterus, which, at 14 weeks, required cerclage for cervical insufficiency. She is undergoing treatment with Clexane for pregnancy thrombophilia with heterozygous factor Leiden V. The pregnancy was correctly monitored and ultrasound revealed a lateral placenta previa that did not cause bleeding during the pregnancy. Her family medical history was without significance for the case.

After hospital admission on 13.07.2022 (Table 1), blood results showed leukocytosis of 14 $\times$ 10^9/L (N 4 $\times$ 10^9/L–10 $\times$ 10^9/L), with 8.8% (20–50%) lymphocytes, 9.9 g/dL (11.5–16 g/dL) Hgb, and 32.4% (35–48%) Htc, therefore indicating moderate pregnancy anemia, along with 51.37 mg/dL (0–5 mg/dL) inflammatory markers modified with PCR, 507.4 g/dL (180–450) fibrinogen, blood group A II, and Rh-positive. In the biochemical tests, the surprise was the uric acid level of 8.98 mg/dL (2.3–6.10 mg/dL) and the patient also developing raised BP of 160/105 mm Hg without having presented hypertension during pregnancy. Proteinuria was 400 mg/24 h. Thus, we considered preeclampsia, with increased uric acid as a sign of possible severe evolution, developed in the case of a patient with thrombophilia as a contributing factor and symptomatic SARS-CoV-2 infection. Ultrasound revealed a live fetus that was well developed according to its gestational age, with appropriate measurements for 35/36 weeks, normal HR, reduced MAF but normal respiratory movements, anterior lateral placenta previa grade II, normal amniotic fluid but with IR ACM = 0.72, and IR Aomb = 0.62 without NOTCH on the uterine arteries as a sign of acute, recently established hypoxia. The patient is under treatment with Clexane 0.6 IU administered subcutaneously, vitamins, and iron tablets. An attempt was made to transfer the patient to a higher-level hospital unit in maternal–fetal interest, but this was without success due to the overlap of the SARS-CoV-2 infection. After discussions with the neonatologists, the decision was made to postpone the delivery, the preterm compartment being occupied, and antioxidant treatment was attempted to reduce the uric acid level, associated with antihypertensive therapy with Nifedipine and Methyldopa. Thus, we

added Allopurinol with a dose of 100 mg/day. During this time, the patient complained of headaches and blurred vision. Cardiotocography is normal. A chest X-ray was not performed because it was not necessary.

Table 1. Blood test results per day.

		Blood Results During Period of Admission Mother						Blood Results Newborn
Tests	**Normal Value**	**13 July 2022**	**14 July 2022**	**15 July 2022**	**22 July 2022**	**26 July 2022**	**27 July 2022**	**26 July 2022**
Leukocytes (WBC)	4.00–10.00 × 10^9/L	14.10 × 10^9/L			10.82 × 10^9/L	12.5 × 10^9/L		24.7 × 10^9/L
Lymphocytes (Lymphs)	1.0–4.1 × 10^9/L	1.2 × 10^9/L			2.27 × 10^9/L	2.05 × 10^9/L		23.0 × 10^9/L
Hemoglobin (HGB)	11.5–16 g/dL	9.9 g/dL			10.5 g/dL	10.9 g/dL		14.2 g/dL
Hematocrit (HCT)	35–48%	32.4%			34.50%	35.8%		44.8%
Platelets (PLT)	150–450 × 10^9/L	280 × 10^9/L			360 × 10^9/L	400 × 10^9/L		213 × 10^9/L
INR	0.8–1.2	0.87			0.94			
APTT	25–38 s	29.9 s			25.9 s			
Fibrinogen	180–450 mg/dL	507.4 mg/dL			789.8 mg/dL			
Creatinine	0.50–0.90 mg/dL	0.70 mg/dL			0.53 mg/dL			
Uric acid	2.3–6.10 mg/dL	7.42 mg/dL	8.98 mg/dL	7.52 mg/dL	5.24 mg/dL		5.44 mg/dL	
GOT/ALT	0.00–31.00 U/I	26 U/I			175 U/I		62 U/I	53 U/I
GPT/AST	0.00–34.00 U/I	21 U/I			388 U/I		171 U/I	15 U/I
C Reactive Protein	0.00–5.00 mg/L	51.3 mg/L			103.83 mg/L		108.8 mg/L	1.68 mg/L
Proteinuria	<150 mg/24 h		400 mg/24 h					
COVID-19 (PCR)	SARS-CoV-2 infection was positive by PCR testing.							Negative by PCR testing
Cultures	All cultures were negative							All cultures were negative

Under treatment with Allopurinol along with antihypertensives, the symptoms improved and the blood pressure normalized. Doppler velocimetry was normalized with IR ACM = 0.82 and IR Aomb = 0.52. Uric acid dropped after one day of treatment to 7.52 mg/dL. LDH was normal at 146 U/l (0–247 U/l) and creatine kinase was normal at 24 U/l (0–145 U/l). The cultures were negative. Fibrinogen increased to 789.8 mg/dL, platelets were normal at 360 × 10^9/L (150–450 × 10^9/L), lymphocytes increased to the normal level, leukocytes decreased, and SARS-CoV-2 symptoms subsided under treatment with vitamins and low doses of anti-inflammatory drugs. The uric acid level decreased to 5.44 mg/dL. In contrast, the inflammatory tests increased, the PCR reached 108.86 mg/L, and the liver tests changed, with GOT of 62 U/l (0–31 U/l) and GPT of 171 U/l (0–34 U/l). the creatinine level remained normal at 0.67 mg/dL (0.5–0.9 mg/dL). On 22 July, GOT was 175 U/l and GPT was 388 U/l, and anemia was corrected, with Hgb of 10.5 g/dL, Htc of 34.5%, and platelets of 360 × 10^9/L; delivery by cesarean section was decided after 12 days of treatment with Allopurinol. We delivered a 2800 gr feminine newborn, Apgar 9. The cerclage was removed. The postsurgical evolution was favorable. The newborn also had favorable evolution, showing no signs of cerebral hypoxia. The cultures were negative. The level of leukocytes was 24,7 × 10^9/L, Hgb was 14.2 g/dL, Htc was 44.8%, platelets were 213 × 10^9/L, mild neonatal jaundice was observed with 4.77 mg/dL indirect bilirubin and 0.67 mg/dL direct bilirubin, negative inflammatory markers were observed, the blood group was AII Rh-positive, and the uric acid level was 5.6 mg/dL. The newborn was negative for SARS-CoV-2 infection by PCR testing. Vaccinations, rickets prophylaxis, and

hemorrhagic disease prophylaxis were conducted. Upon follow-up, we observed normal neurological development.

In Table 1, we can follow the changes in the laboratory values under the proposed treatment during hospitalization, and we must mention here that Allopurinol was administered only for the first five days. In the figures, we can better see how uric acid normalized (Figure 1), and the liver (Figures 2 and 3) and inflammatory tests (Figures 4 and 5) increased, the latter at a lower speed after administering Allopurinol.

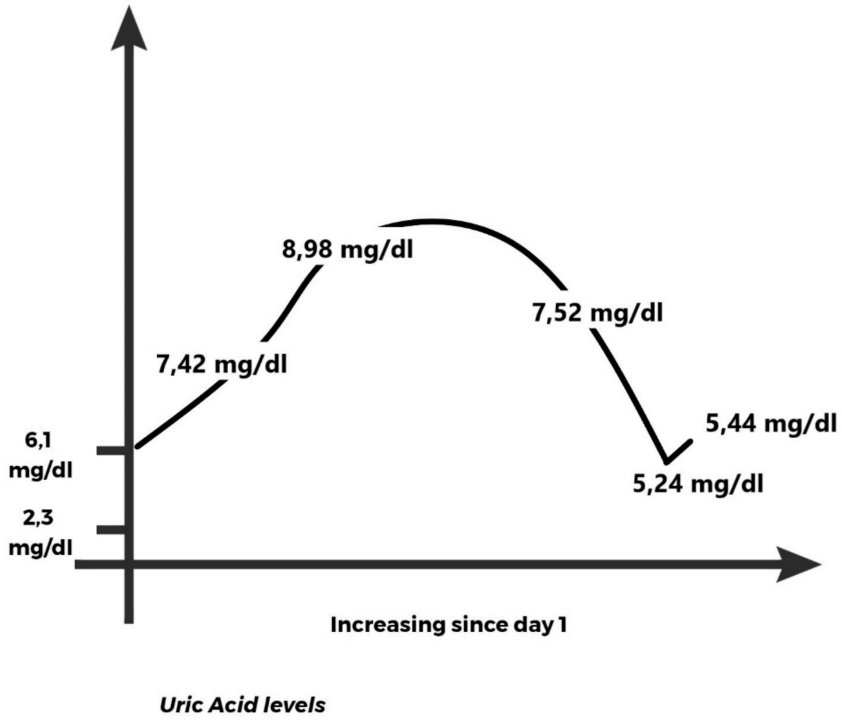

Figure 1. Changes in the uric acid levels.

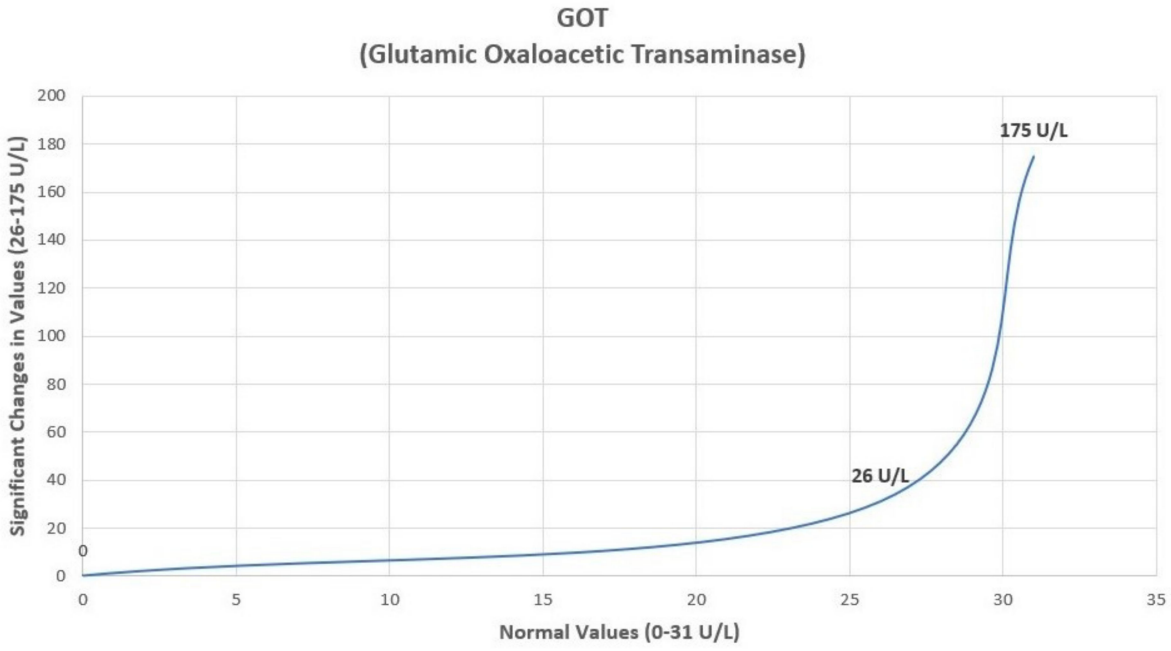

Figure 2. Significative changes in the GOT.

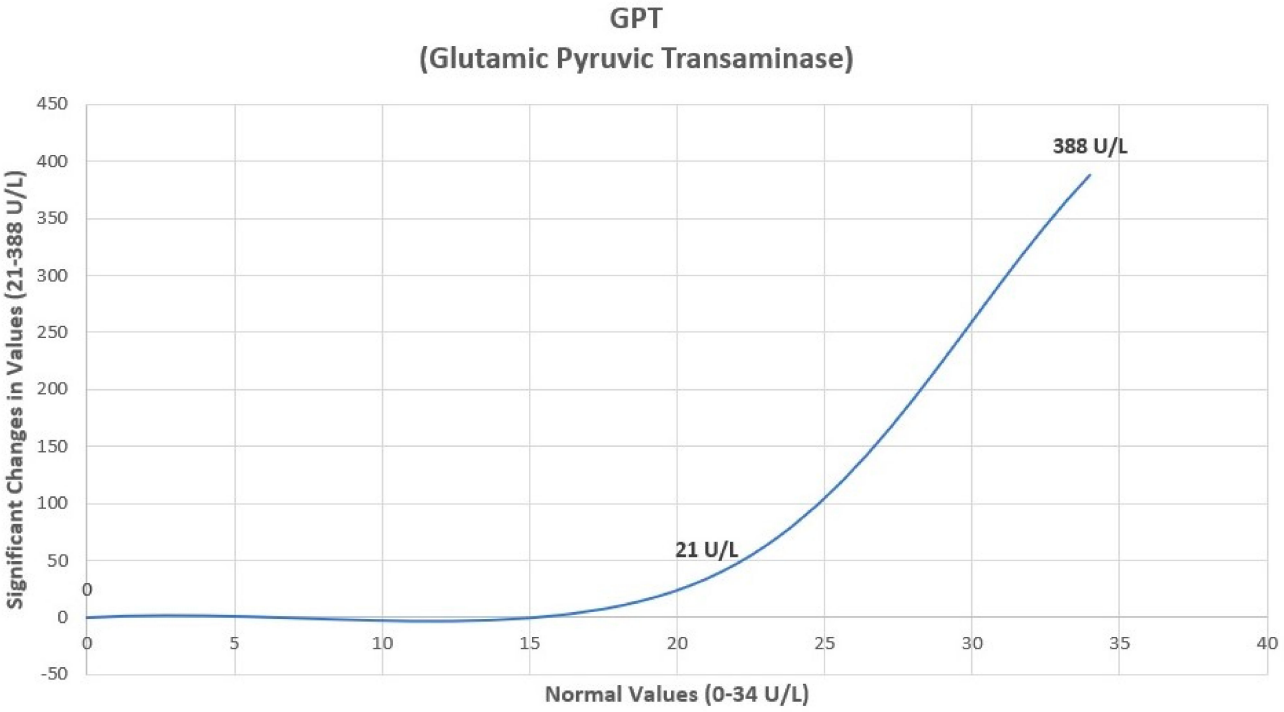

Figure 3. Significative changes in the GPT.

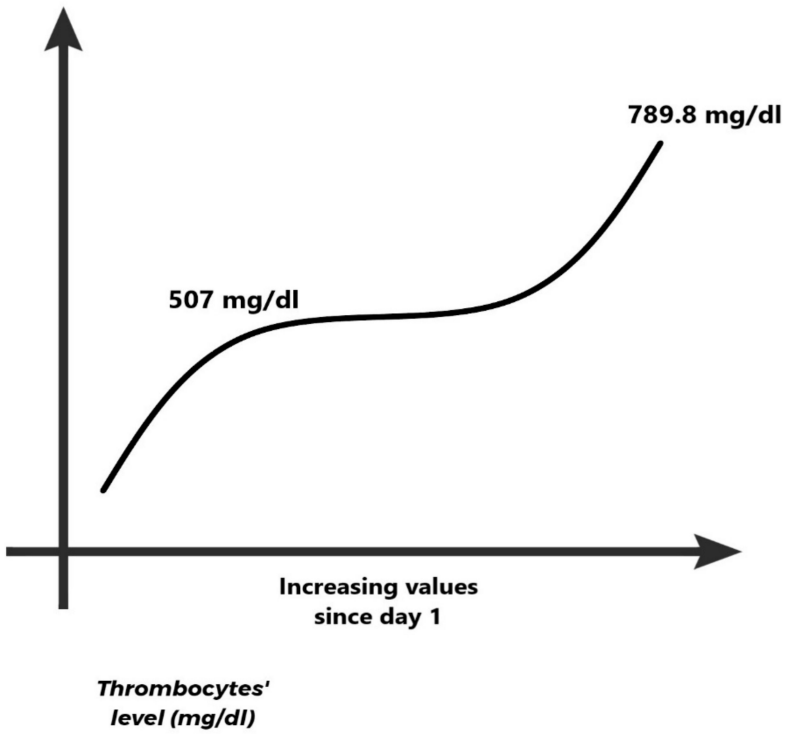

Figure 4. Changes in the thrombocyte level.

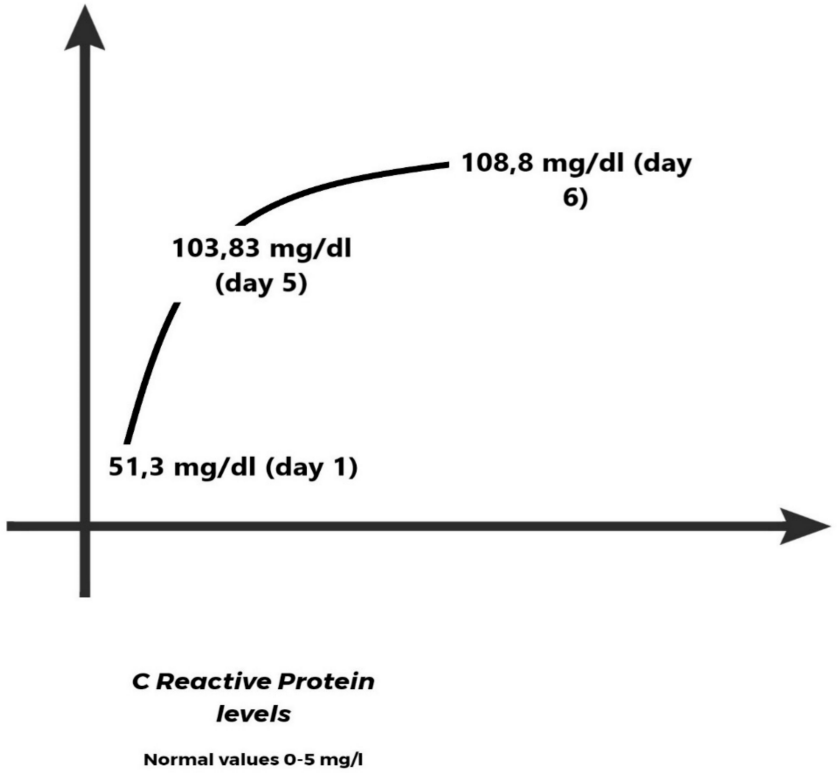

Figure 5. Changes in the C-reactive protein levels.

3. Discussion

Hyperuricemia is rare in pregnancy, under the effect of estrogen, because it causes increased glomerular filtration. In preeclampsia, hyperuricemia appears because of its production in increased amounts in the ischemic–hypoxic placenta [8,10].

The association of preeclampsia with hyperuricemia has been known since 1917. Its role in the severity of PE was described for the first time in 1934 and it is a useful tool in maternal–fetal prognosis [10,24]. The severity of PE could be quantified by the peripheral blood value of uric acid. A higher level can trigger a cascade of inflammation and oxidative stress with negative consequences for both the mother and fetus [6,8,12,25], something also observed in our case (Figure 1).

The clinical consequences of severe preeclampsia are manifested by headaches, nausea, convulsions, placental abruption, HELLP syndrome (hemolysis, liver, low platelet), intravascular dissemination, stroke, and kidney failure. The main cause is arterial hypertension and endothelial damage [9,26,27]. In newborns, severe preeclampsia is accompanied by IUGR (intrauterine growth restriction), fetal asphyxia, hypoxic–ischemic encephalopathy, premature birth with acute respiratory distress syndrome, and a low APGAR score at birth [9,10,27,28]. Uric acid and ROS are involved in causing fetal brain damage [9,27]. Additionally, perinatal mortality is about 10% and maternal mortality is about 10–15% [24].

In addition, our patient experienced infection with SARS-CoV-2. The impact of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection on pregnant women is similar to that on the general population: pregnant women with comorbidities are more affected, according to the literature [13,14]. In addition, Gabrieli et al. described the occurrence of thromboembolic events as another consequence of SARS-CoV-2 infection [17]. Pregnancy has an adaptive mechanism to reduce the risk of hemorrhage during and after the delivery process. Low-molecular-weight heparin (LMWH) once again proved its effectiveness [17], which is available and accepted as a therapy during pregnancy. In our case report, the findings regarding this disease were similar to the findings reported from the literature. The patient did not experience severe pneumonia; she manifested some coagulation disorder, but she was also under LMWH treatment already because of

thrombophilia. Regarding other obstetric complications, in the literature, an increase in the rate of cesarean delivery and fetal hypoxia correction after birth are described [16], another motivator to use Allopurinol as an effective antioxidant.

Allopurinol, when used to reduce the level of uric acid, also has an antioxidant effect in severe preeclampsia. This medicine has a role in preventing HELLP syndrome, eclamptic seizures, renal disease, cardiac failure, or strokes [9,26,27,29]. There are studies in the literature about its effectiveness on newborns [30]. It prevents prematurity, acute respiratory distress syndrome, and hypoxic–ischemic encephalopathy [9,10,27,31–33]. It has proven its effectiveness only before chronic brain damage, leukomalacia, occurs [9,10,27].

Regarding the side effects, skin reactions have been reported. They could be severe Allopurinol hypersensitivity reactions, depending on the dose, sometimes accentuated by renal failure. In this severe condition, plasmapheresis can help [33–39]. Teratogenicity was also discussed, if used in the first trimester of pregnancy. Abnormalities discovered in rats were 3,8%, compared with 3% in the general population, but are still to be considered [9,25,39–41].

Allopurinol has proven its usefulness as an antioxidant and against uric acid production. It has a role in protecting the fetus from neurological damage associated with hypoxic-ischemic encephalopathy. In this article, we present the option of Allopurinol treatment in preeclampsia regarding both the mother and fetus.

By adding Allopurinol to the antihypertensive treatment in small doses for a short period of time in the third trimester of pregnancy, the complications of severe preeclampsia were avoided. Abruptio placentae, premature birth, stroke, eclampsia, as well as the complications of a newborn, born with an Apgar score of 9, without respiratory distress, neonatal asphyxia, or hypoxic–ischemic encephalopathy were prevented. We can associate the onset of severe preeclampsia with symptomatic SARS-CoV-2 infection and with the presence of thrombophilia. This is aggravated by the increase in uric acid with the onset of the first signs of oxidative stress detected by Doppler velocimetry and the reduction in active fetal movements. The decision to initiate treatment with Allopurinol was lifesaving, preventing premature extraction of the newborn from a pregnancy with rapidly developing severe preeclampsia associated with SARS-CoV-2 infection. All the complications that would result from a premature birth decision were prevented. We kept in mind that delivery was the only proven efficient treatment in the case of severe preeclampsia.

Placental pathological examinations should be included in future study designs to obtain more information about the preeclamptic lesions that may occur.

The weak point of this study is that it is an observational study. Allopurinol therapy to improve severe preeclampsia is not routinely recommended at this time. There is a limitation in the literature due to the heterogeneity of the data and the small number of patients included in studies. The link between uric acid and the severity of preeclampsia is not completely understood. Additionally, the correlation of the plasma uric acid level with Doppler velocimetry is yet to be demonstrated. Teratogenicity was observed based more on case reports. Limited data regarding Allopurinol administration in the third trimester of pregnancy are available in the literature, but suggest a safe profile [29]. Biomarkers useful for screening preeclampsia were also not sought, such as placental growth factor PIGF.

The strong point of our case is that Allopurinol proved its effectiveness in preventing the complications of severe preeclampsia and of premature birth. We used the uric acid level in the third trimester of pregnancy as a valuable biomarker with applicability in clinical practice [3]. It is useful, along with Doppler velocimetry, to identify patients considered at risk in order to initiate antioxidant therapy with an effective dosage. Additionally, it must be considered that Allopurinol crosses the placenta and can reach therapeutic levels in fetal blood. This could be a way to prevent cerebral hypoxic damage in newborns [31]. Of course, it is mandatory to find the correct dosage and administration should be reduced to short periods of time, and it should be a niche drug that accompanies antihypertensive drugs. The recommendation is to use this drug for the prevention of fetal hypoxia, premature birth, or other complications of preeclampsia.

We do not recommend Allopurinol as a useful drug in COVID-19 infection, but it definitely improved the condition of the patient and the fetus in preeclampsia. For COVID-19, some authors prescribed cell therapy as a possible treatment [32]. More studies would be necessary.

4. Conclusions

The new acute respiratory syndrome-related coronavirus 2, or SARS-CoV-2, causes a variety of manifestations, such as multiorgan failure; however, in our case, there was no need for antiviral treatment, but anticoagulants proved effective. From an obstetrical point of view, a cesarean section was performed on the patient.

A study would be necessary to learn how we can extend the duration of pregnancy, using Allopurinol as antioxidant therapy, safely for the mother and fetus. This would be necessary until the condition of the fetus allows survival without complications after birth. Birth is the only effective therapy known in preeclampsia so far.

Placental pathological examination could provide useful information about the mechanism of preeclampsia.

This being said, new studies and a better follow-up of pregnancies and newborns treated with Allopurinol are recommended.

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