# Essential mixed type II cryoglobulinemia in a HCV positive pregnant woman: case report

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**Summary**

Cryoglobulins are a group of proteins with the common property of precipitating from cooled serum. Cooled cryoglobulinemia is a classic disease caused by immune complexes which subside on vessel walls and produce a clinical picture represented by recurrent purpura, asthenia, arthralgias, Raynaud's phenomenon, glomerulonephritis and sensorimotor neuropathy. The authors describe a case of a patient C.M., 37 years old, with cryoglobulinemia, chronic hepatitis C and gravidic cholestasis at 28 weeks' gestation. The clinical picture worsened with the appearance of mild hypertension with proteinuria and hypochromic anaemia. At 31 weeks' the arthralgic symptomatology and pruritus revealed degeneration with an alteration of glycemic profile values and treatment with rapid human insuline was started. The cardiotocography began to be pathologic and a cesarean section was performed; the newborn weighed 1570 g. Cooled cryoglobulinemia is a pathology which worsens in a gravidic state and can impair the outcome of pregnancy.

*Key words:* Cryoglobulinemia; HCV; Pregnancy.

## Introduction

The term "cryoglobulin" is used to describe a group of proteins with the common property of precipitating from cooled serum [1]. Brouet *et al.* [2] identified three types of cryoglobulins. Type I consists of monoclonal immunoglobulins without rheumatoid factor activity that are associated with malignant conditions of the immune system. Type II consists of polyclonal IgG and monoclonal IgM rheumatoid factor. Type III consists of polyclonal IgG and IgM. These last two types are defined mixed cryoglobulins. Clinically, mixed cryoglobulinemia has been classified as essential if there is no primary disease other than Sjogren's syndrome and secondary if it is in association with chronic liver pathology, infections, autoimmune disease, and malignant neoplasms [3]. Levo *et al.* suggested that HBV was involved in the pathogenesis of essential mixed cryoglobulinemia [4-6]. Agnello *et al.* [3] reported the detection of hepatitis C virus RNA with type II cryoglobulinemia. The correlation between cryoglobulinemia and HCV is tempered by the high prevalence of HCV antibodies without demonstrable infection in the other autoimmune diseases that cause hepatocellular injury [7]. Cryoprecipitation is responsible for acute, recurrent purpura, asthenia, arthralgias, Raynaud's phenomenon, glomerulonephritis and sensorimotor neuropathy [2]. Sometimes, the clinical picture gets worse with vascular insufficiency, renal failure and progressive involvement of the peripheral nerves [8]. There is also rheumatoid factor activity and normochromic normocytic anaemia [9]. In the past, the treatment consisted of plasmapheresis or plasma exchange plus corticosteroids or cytotoxic drugs [8]; today favourable results with a treatment of mixed cryoglobulinemia and alpha interferon are encouraging [10]. In most cases this pathology involves the female and male population aged from 43 to 76 years [9]. We describe a case of a patient, C.M., 37 years old, with cryoglobulinemia in pregnancy.

## Case Report

Beginning in 1982 the patient had shown signs of hepatopathy. In 1991 she underwent liver biopsy and a diagnosis of chronic hepatitis C and symptomatic cryoglobulinemia was made. In October 1995 the patient was hospitalized at 22 weeks' gestation due to onset of extended itching. The hematochemical parameters showed an increase of biliary salts with a mild transaminase rise. About 1% of cooled cryoglobulins were present which became ~10% at 31 weeks' of pregnancy (Table 1). The regimen, based on administration of Adenosine-Methionine orally, aspirin 100 mg/day, Dexamethasone and vitamin K, produced an improvement in the patient's clinical state. At 31 weeks' of pregnancy a worsening of cryopathic purpura was observed with the reappearance of arthritis and coexistence of substantial itching caused by gravidic cholestasis. A 10% of cryocrit with a significant increase of rheumatoid factor in serum, even at room temperature, and a decrease of complement was observed (Table 1). Therefore a higher dose of Dexamethasone up to 10 mg/day for five days in a week was given. At 33 weeks' gestation, having a marked exacerbation of symptomatology and an estimated fetal weight of 1800 g, an elective cesarean section was performed and a male newborn weighing 1770 g in good health was born. A few days after delivery, the cryopathic and cholestasic symptomatology decreased and the patient was discharged and informed about how to avoid another pregnancy. The newborn was discharged in good health after 43 days in the Neonatal Intensive Care Unit (I.C.U.). However, in October '96 she again came under our care for gravidic cholestasis at 28 weeks' gestation. Hematic values showed a significant increase of biliary salts, γGT, transaminase and glycosilated haemoglobin. The complement's fraction was

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under threshold while about 1% of cooled cryoglobulins were present (Table 2). The patient complained of an intense itchy symptomatology with the appearance of general scratch lesions. From the beginning of pregnancy she was in therapy with Methylprednisolone 8 mg/day (five days in seven). The clinical picture worsened with the appearance of mild hypertension and light proteinuria and hypochromic anaemia. Dermatologic lesions suggested a primitive vasculitic component linked to cryoglobulinemic syndrome. Observing a worsening of her general condition at 29 weeks' and 4 days' of pregnancy, we administred Dexamethasone, 12 mg/day, to obtain pulmonary fetal maturation, followed by Prednisone, 12.5 mg every 3 days. At 30 weeks' of pregnancy due to an increase of mean arterial pressure, therapy with a slow releasing Calcioantagonist, 30 mg/day, was started. At the same time extended arthralgic symptomatology began to appear. At 30 weeks' and 5 days', this same symptomatology showed a remarkable worsening and a sudden increase of glycemic profile values (Table 3); so a treatment with rapid human insuline was started. Even with the administration of insuline's bolus, there was no improvement in glycemic values; the fetal condition worsened and cardiotocography began to be pathologic. Thus, it was decided to perform an elective cesarean section, with the birth of a male weighing 1570 g and with an Apgar score of 8-10. The patient in the post-operative period was led to I.C.U. and after a few hours she showed normalization of glycemic and pressor values. In the following days the general symptomatology regressed and the patient was discharged. The infant (HCV negative) was discharged from the Neonatal Intensive Care Unit after 54 days in a good state of health. As for hepatitis C, we should point out that the patient had shown a HCV-RNA positivity tested with PCR-nested. Her infants have not contracted the infection, showing a regression of anti-HCV antibodies in 9 months.

Table 1. — *Hematochemical parameters of the first pregnancy.*

| | 22 weeks' gestation | 31 weeks' gestation |
|---|---|---|
| Irregular antibodies | | negative |
| Anticardiolipin antibodies | < 23 | |
| Antinuclear antibodies | Negative | |
| Antithyroid antibodies | Negative | |
| Transaminase | GOT 69; GPT 57 | |
| C3 | 61 mg% | 48 mg% |
| C4 | 1.9 mg% | 4 mg% |
| Cryoglobulins | 1% | 10% |
| Biliary salts | 55 Moli / l | |
| Rheumatoid factor | | 113 |

Table 2. — *Hematochemical parameters of the second pregnancy.*

| | |
|---|---|
| Biliary salts | 54.2 Moli / l |
| GT | 98 U/L |
| GPT | 38 U/L |
| GOT | 49 U/L |
| HbA1c | 6.02% |
| Anticardiolipin antibodies | < 23 U.A. |
| Antinuclear antibodies | negative |
| Anti DNA antibodies | negative |
| Cooled cryoglobulins | 1% |
| Protidaemia | 5 mg/dl |
| C3 | 66 mg/dl |
| C4 | < 9 mg/dl |

Table 3. — *Glycemic profile values and therapy in the second pregnancy.*

| 30 + 5 weeks' gestation | Glycemia | Therapy |
|---|---|---|
| h 8.00 | 295 | |
| h 11.00 | 220 | |
| h 14.00 | 202 | |
| h 17.00 | 161 | |
| h 20.00 | 167 | |
| h 23.00 | 153 | |
| **30 + 6 weeks' gestation** | **Glycemia** | **Therapy** |
| h 2.30 | 152 | Humulin R 3 U.I. s.c. |
| h 5.30 | 175 | |
| h 8.00 | 135 | |
| h 12.30 | 178 | Humulin R 5 U.I. s.c. |
| h 14.00 | 211 | |
| h 15.00 | 324 | Humulin R 6 U.I. s.c. |
| h 16.40 | 347 | Humulin R 7 U.I. s.c. |
| h 17.40 | 484 | Humulin R 10 U.I. i.v. |

## Discussion

The particularity of this case is the young age of our patient if we consider the age in which this pathology usually appears. Cooled cryoglobulinemia is a classic disease caused by immune complexes which subside on vessel walls and produce a clinical picture represented by palpable purpura. In the glomerule they can cause glomerulonephritis with a reduction of renal functioning. This anatomicopathological aspect is particularly important in pregnancy since functional renal deficiency can give rise to a gestosis syndrome. Additionally, these vascular alterations can produce a coagulation disorder with an imbalance in the thromboxan/prostacyclin ratio and so favour the onset of a pregnancy-induced hypertension. Vascular damage can spread to placental vessels with flow restriction and rebound on the fetus whether affecting fetal growth or oxygenation. This complex etiopathogenetic picture has awakened a particular interest due to the rapid clinic evolution, above all in the second pregnancy. In fact, the endothelial vascular damage produced a mild-severe pre-eclampsia after a few days hardly ruled by hypotensive therapy, and a disorder of glucose metabolism. The last one speeded up the cortisone treatment, necessary for improvement of cryoglobulinemia or for fetal pulmonary maturation. In our case no fetal growth retardation, which is more apparent beginning at 28-30 weeks' of pregnancy, was seen. In the second pregnancy the acute progression of the clinical picture certainly conditoned fetal oxygenation and this appeared by anomalies of cardiotocography. Thus, we can say that cooled cryoglobulinemia is a pathology which worsens in a gravidic state and can impair the outcome of such pregnancy. Pregnant patients with cryoglobulinemia need to be carefully monitored in specialized centers. In our opinion it is correct to forestall delivery, even with a cesarean section, until an increased risk of decompensation of maternal disease is manifest and with careful monitoring of renal and hepatic functions and glucose metabolism.

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