



Safe use of rituximab in a pregnant woman with Henoch-Schonlein purpura

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Abstract

Rituximab is a monoclonal antibody that targets CD20 on peripheral B cells, depleting them from the circulation and consequently decreasing disease activity. Regarding the safe use of rituximab during pregnancy, it has been shown that significant placental passage of rituximab occurs starting week 16 potentially affecting the development of fetal and neonatal B-cells, and leading to increased predisposition to infections. We describe the first case in Henoch-Schonlein purpura of maternal exposure to rituximab shortly before conception. Follow up neonatal immune studies demonstrated normal B-cell counts and immunoglobulin levels without any serious infectious complications. Given the facts that data from animal studies are inadequate, human studies are lacking, and rituximab is detectable in serum of neonates for up to 6 months, rituximab carries an FDA Pregnancy Category C and is not recommended during pregnancy or lactation. However, based on our case report, together with published cases, it is suggested that rituximab exposure soon before conception or during pregnancy, does not carry serious immunologic effects on the neonate.

Key words: Rituximab, Biologic therapy, pregnancy, vasculitis, safety, Henoch-Schonlein purpura, B-cell.

Dear Editor,

Rituximab is a chimeric (murine/human) monoclonal antibody that targets CD20 on peripheral B cells, depleting them from the circulation and consequently decreasing disease activity.^[1]

Not many data have been published regarding the safe use of rituximab during pregnancy. For instance, studies carried out on rituximab in non-human primates did not demonstrate fetotoxicity. However, they have shown that significant placental passage of rituximab occurs starting week 16 to become extensive in the third trimester and achieve fetal serum levels comparable to maternal levels.^[2-4] This might potentially affect the development of fetal and neonatal B-cells leading to increased predisposition to infections, as was shown in the offspring

of cynomolgus monkeys exposed during pregnancy to therapeutic doses of rituximab, which had reduced B cells that returned to normal within 6 months after birth.^[5] Given the facts that data from animal studies are inadequate, human studies are lacking, and rituximab is detectable in serum of neonates for up to 6 months, it is recommended that women of childbearing potential use contraception during treatment and up to 12 months after exposure.^[6]

We describe the first case in Henoch-Schonlein purpura (HSP) of maternal exposure to rituximab 2 months prior to conception and present a review of the literature of cases and studies conducted on rituximab exposure during pregnancy.

A 32-year-old gravid 3, para 3, aborta 0 woman with chronic HSP

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was poorly controlled with steroids and azathioprine. Her disease was recurrently manifesting with diffuse skin lesions consistent with leukocytoclastic vasculitis, in addition to recurrent upper and lower gastrointestinal bleeds with vasulitic changes seen on endoscopy since 2009. Due to her active disease, she was treated with two doses of rituximab, 1000 mg each, two weeks apart in April 2010, on which she had good clinical response manifested by resolution of the skin lesions and gastrointestinal bleeds. The patient was not using oral contraceptives, and she reported an established pregnancy two months after the rituximab infusion. Following an uncomplicated pregnancy of 39 weeks, she delivered a healthy boy by normal vaginal delivery. Immune studies performed at 3 months of age and repeated at 8 months after completing the required immunizations, showed no evidence of immunodeficiency, as normal B-cell counts and immunoglobulin (Ig) levels were measured except for a low IgA seen at 8 months (Table 1). Anti-Hepatitis B surface antigen antibodies were positive in response to vaccination. On complete blood count, mild microcytic anemia was seen (Hb 11.3 g/dL, MCV 67.0 fl), which was explained by the lack of iron supplementation at 6 months of age. Other hematological tests were normal. The baby has met developmental, cognitive and behavioral milestones appropriate for his age, assessed using DENVER II and growth charts, and he did not manifest any serious infectious diseases that required hospitalization or that are beyond what is commonly encountered in infants. A literature review was performed using PubMed database by searching the terms rituximab, pregnancy and vasculitis; only English articles with full text available were included. In a recently published study on maternal exposure to rituximab, 231 registered pregnancies on the rituximab global drug safety database were analyzed.^[7] 153 out of the 231 pregnancies had a known out-

come, where 90 resulted in live births, of which 22 were born prematurely; with one neonatal death at 6 weeks. Eleven infants suffered hematological abnormalities without infectious complications, two infants had congenital anomalies and four complained of neonatal infections (fever, bronchiolitis, cytomegalovirus hepatitis, and chorioamnionitis). Also, there was one reported maternal death due to pre-existing autoimmune thrombocytopenia. However, concomitant exposure to other potentially teratogenic medications and underlying maternal illness confounded the findings of the presented cases.^[7] Moreover, a number of case reports have been published regarding maternal exposure to rituximab during pregnancy, mostly in combination chemotherapy for the treatment of malignancies or severe nonmalignant hematologic abnormalities.^[8] Because of the limited number of these cases and the fact that B-cell counts were not measured in all of them, no relation can be drawn between underlying disease and abnormal B-cell counts in the neonates. However, knowing that rituximab remarkably crosses the placenta starting the second trimester,^[2-4] a relation can be suspected between decreased levels of neonatal B-cells and timing of rituximab administration; in three of four cases with depleted neonatal B-cells, rituximab exposure was in second and third trimester; and, in the fourth case, depletion occurred following administration in first trimester, where rituximab levels could have persisted.^[8] On the other hand, in three reported cases of normal B-cell counts, rituximab exposure occurred before the second trimester,^[8] similar to our presented case. Moreover, in two out of five cases where rituximab was administered in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP), neonatal B-cell abnormalities were observed.^[8] However, case reports have shown that the administration of CHOP during pregnancy is not associated with an

Table 1. Immune profile at 3 and 8 months of age.

Age	Immunoglobulins (Ig), Quantitative (g/L) [reference range for age]		
	IgG	IgA	IgM
3 months	4.01 [1.76-5.81]	0.34 [0.046-0.46]	0.77 [0.24-0.89]
8 months	5.09 [2.17-9.04]	0.00672 [0.11-0.9]	0.83 [0.34-1.26]
Age	*CD19+ (Value/Absolute count) [reference range for age]		
3 months	1,311.53 [120-2,100]		
8 months	1,777.71 [20-2,300]		

*Marker of B-cells.

increase risk of fetal abnormalities.^[9] Hence, the abnormal B-cell counts observed in the aforementioned cases can be attributed to rituximab rather than to CHOP.

Generally, fetal outcomes in these situations were favorable as B-cell counts recovered without serious infections in all affected infants. This can be attributed first to B-cell precursors that were not affected by rituximab, and which led to the rapid B-cell recovery observed in infants; and second, to the protective role played by maternal immunoglobulins in defending against serious neonatal infections. Similar to our presented infant, case reports showed that antenatal exposure to rituximab did not affect neonatal immunoglobulin levels, as all cases demonstrated a positive response to vaccination, a natural test for B-cell function.^[8]

Regarding the safety of rituximab use in pregnancy, not much has been published, and long-term studies on immune function (B cell counts) in infants exposed in utero are still lacking.^[10] For this reason, rituximab carries an FDA Pregnancy Category C and is not recommended during pregnancy or lactation. However, based on our case report, together with published cases, rituximab exposure soon before conception or during pregnancy may not carry serious immunologic effects on the neonate.

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