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Intravenous Iron Given prior to Pregnancy for Restless Legs Syndrome is Associated with Remission of Symptoms

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CASE REPORTS

Restless legs syndrome (RLS) is more common during pregnancy than in the general population, occurring at a 2-3 times higher prevalence. While iron, genetics, and central nervous system dopamine have been shown to play major roles in RLS unrelated to pregnancy, the etiology and treatment of RLS during pregnancy have not been adequately delineated. We describe a novel approach where a 23-year-old female was given intravenous iron prior to pregnancy, with complete remission of RLS symptoms until five months postpartum. Factors other than iron status that may have influenced the course of remission and relapse were oral contraceptive use, antidepressant use, and a strong family history of RLS.

Keywords: Restless legs syndrome, pregnancy, iron, intravenous iron, Willis-Ekbom disorder, depression

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Restless legs syndrome (RLS), also known as Willis-Ekbom disorder, is 2-3 times more prevalent during pregnancy than in the general population,[1-4] with peak prevalence in the third trimester and resolution of symptoms for many by one month after delivery.[1] Independent predictors of RLS during pregnancy are a past history of RLS when not pregnant, a family history of RLS, a history of RLS during prior pregnancy, and hemoglobin ≤ 11 g/dL.[2] Preexisting RLS also predicts greater severity during pregnancy than before pregnancy.[3] More than half of women affected during pregnancy report severe or very severe RLS symptoms.[4]

REPORT OF CASE

A 23-year-old female presented for management of chronic, moderate-to-severe RLS prior to becoming pregnant. Diagnosis was at age 19, but she recalled RLS symptoms since early childhood. Family history was positive for moderate-to-severe RLS with periodic limb movements in sleep (PLMS) affecting her biological mother and younger sister. For one year prior to the visit the patient reported consistently bothersome RLS symptoms that occurred most nights, associated with sleep disturbance, daytime fatigue, and PLMS observed by her husband. She took citalopram 20 mg/day because of depression with anxiety and panic attacks since age 16 years, with good control of those symptoms. The patient was also on levonorgestrel/ethinyl estradiol and ferrous sulfate (65 mg elemental iron). Oral iron had been started 3 months prior to the visit when her serum ferritin was low at 15 mcg/L. At the initial visit ferrous sulfate was replaced with extended-release iron due to gastrointestinal discomfort (daily dose 100 mg elemental). In addition, citalopram was replaced with fluoxetine 20 mg/day, because more is known about its use during pregnancy.

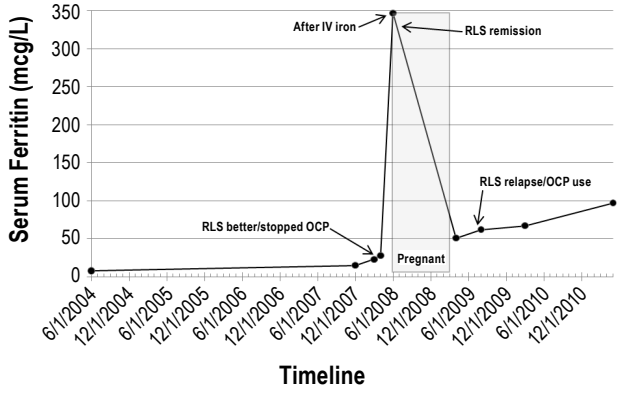
One month later ferritin had increased to 23 mcg/L, but 1.5 months after that was only 28 mcg/L with a high total iron binding capacity of 527 mcg/dL (normal 250-400) and borderline low saturation of 15% (normal 15-50), indicating ongoing iron deficiency; hemoglobin was 14.8 g/dL (normal 11.0-16.0). However, RLS symptoms were notably improved with these changes and concurrent discontinuation of the oral contraceptive pill (OCP) for planned pregnancy (**Figure 1**). Nonetheless, because of concern about potential worsening of RLS during pregnancy and limited progress in improving her iron status with oral iron, intravenous iron sucrose 1,125 mg was given in 5 treatments over 7 days. She became pregnant the week following the last treatment. Ferritin rose to 347 mcg/L, and RLS symptoms remitted completely within 1 month of intravenous iron.

The patient remained on fluoxetine and took a daily prenatal vitamin during the pregnancy, delivering a healthy, full-term girl by caesarean section. At a sleep clinic visit 7 weeks postpartum, she reported continued full remission of RLS symptoms and full control of depression and anxiety; ferritin was 51 mcg/L. She resumed daily oral iron (100 mg elemental). However, 5 months postpartum with ferritin at 62 mcg/L, RLS symptoms relapsed coincident with restarting of the OCP. Nonetheless, RLS symptoms were mild and manageable over the following 2 years with ferritin in the 60-100 mcg/L range (**Figure 1**). She remained on fluoxetine (20 mg/day), iron, and the OCP, with good control of depression and anxiety as well.

DISCUSSION

The etiology of RLS during pregnancy has not been adequately defined.[5] Although there is convincing evidence for a major role of iron deficiency in the pathophysiology of RLS for non-pregnant individuals, and demands on iron stores during

Figure 1—Serum ferritin levels before, during, and after first pregnancy of a young woman with preexisting moderate-to-severe RLS



RLS, restless legs syndrome; IV, intravenous; OCP, oral contraceptive pill.

pregnancy are significant,[6] serum ferritin levels have *not* been found to be lower in pregnant women with RLS compared to controls.[7-9] Also, the rapid improvement in RLS postpartum is difficult to account for by total iron stores, which typically remain low postpartum.[6-8] However, iron availability may be as important as total iron stores. Postpartum, maternal red blood cell (RBC) mass contracts and approximately 450 mg of iron rapidly becomes available for other uses.[6] During pregnancy, the developing fetus and placenta, as well as expanding maternal RBC mass, draw down iron stores *and* compete with other tissues for iron, potentially decreasing availability to the brain of the remaining stored iron.[6] Lower ferritin levels prepartum suggest that women who develop RLS start out at a disadvantage.[9] In addition, lower hemoglobin during pregnancy[2,7] suggests that women with RLS during pregnancy may be at a disadvantage in the competition for iron. Treatment with iron before pregnancy can boost brain iron before there is intensified competition for available iron.

Estrogen has been postulated as a factor for RLS during pregnancy but evidence is conflicting.[7,8] Recently, a prospective study found estrogen use to be an independent risk factor predicting incident RLS in women.[10]

This case illustrates some interesting issues regarding the possible etiology and treatment of RLS related to pregnancy. While intravenous iron administration and a rise in serum ferritin to 347 mcg/L were associated with full remission of RLS, RLS symptoms had improved significantly prior to that coincident with a modest rise in ferritin from 15 to 28 mcg/L, coupled with discontinuation of an OCP and switching from citalopram to fluoxetine.[11] Surprisingly, there were no RLS symptoms during the second or third trimester. However, mild relapse occurred five months postpartum coincident with resumption of the OCP, despite a ferritin level of 62 mcg/L and no other changes in medication. Overall, these findings suggest benefit from intravenous iron prior to pregnancy but that more than one factor may mediate the expression of RLS.

Iron treatment for non-pregnancy, "idiopathic" RLS is typically recommended when serum ferritin is below 50 mcg/L, based on the results of placebo-controlled oral and IV iron trials.[12] This is in contrast to the "normal" range of 11-307 mcg/L when considering treatment for iron deficiency anemia. However, there are no specific guidelines for iron treatment of RLS during pregnancy. In this case of known, moderate-to-severe RLS we chose to boost iron stores prior to pregnancy with IV iron, when oral iron was not successful in raising serum ferritin to above 50 mcg/L.

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