

# Disease-Modifying Drug Possibly Linked to Placental Insufficiency

## Severe placental complications in a pregnant woman with multiple sclerosis

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### الأدوية المغيّرة للمرض قد تؤدي إلى قصور المشيمة مضاعفات حادة في مشيمة امرأة حامل ومصابة بمرض التصلب المتعدد

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**ABSTRACT:** Disease-modifying drugs (DMDs) such as interferon (IFN)- $\beta$  and glatiramer acetate are often prescribed to slow disability progression in patients with multiple sclerosis (MS). However, adverse pregnancy outcomes have been reported with these medications. We report the rare occurrence of severe placental complications in a 30-year-old pregnant woman with MS who continued to take IFN- $\beta$  during her first trimester. She presented at the Tawam Hospital, Al Ain, United Arab Emirates, in 2013 with early-onset fetal growth restriction. At 30 gestational weeks, she developed severe pre-eclampsia. The baby was delivered via emergency Caesarean section and was discharged at the age of two months. Continuation of IFN- $\beta$  during pregnancy may have contributed to the development of placental insufficiency in this patient. Increased education regarding the risks of DMDs for pregnant patients with MS is very important to ensure successful pregnancy outcomes.

**Keywords:** Multiple Sclerosis; Interferon Beta; Pre-Eclampsia; Fetal Growth Retardation; Placental Insufficiency; Case Report; United Arab Emirates.

**الملخص:** يعتبر عقاري البيتا انتيرفيرون واسيتات الجلتيمرات من الأدوية المستخدمة لإبطاء الإعاقة في مرضى التصلب المتعدد، وهناك تضارب في البيانات الخاصة بتأثير هذه الأدوية علي الحمل، هذا تقرير حالة عن حدوث مضاعفات شديدة في مشيمة امرأة حامل في الثلاثين من العمر مصابة بمرض التصلب المتعدد، حضرت المريضة لمستشفى توام بالعين في الإمارات العربية المتحدة عام 2013م مع نقص مبكر في نمو الجنين، في الأسبوع الثلاثين من الحمل تعرضت المرأة لمضاعفات الحمل وتم توليد الطفل بشكل طارئ عن طريق العملية القيصرية، وتم ترخيص الطفل بعد شهرين، إن استمرار تعاطي عقاقير المرض في الثلاثة شهور الأولى من الحمل أدى ذلك إلى حدوث قصور في المشيمة، يجب الإهتمام بتثقيف وتوعية المرضى المصابين بالتصلب المتعدد عن هذه المخاطر من أجل نتائج ناجحة للحمل.

**كلمات مفتاحية:** التصلب المتعدد؛ انترفيرون بيتا؛ اسيتات الجلتيمرات؛ تسمم الحمل؛ تأخر نمو الجنين؛ قصور المشيمة؛ تقرير حالة.

**M**ULTIPLE SCLEROSIS (MS) IS A CHRONIC demyelinating neurological disease resulting from the predominately T cell-mediated autoimmune destruction of oligodendrocytes which synthesise myelin.<sup>1</sup> The disease affects women twice as often as men and symptoms usually present when patients are between 20 and 40 years old, which means that women of reproductive age are the most susceptible.<sup>1</sup> Several disease-modifying drugs (DMDs) have been reported to reduce the frequency of clinical MS attacks and are prescribed with the intent of slowing disability progression; these medications include interferon (IFN)- $\beta$  1a and 1b, glatiramer acetate, natalizumab, mitoxantrone and fingolimod, with IFN- $\beta$  and glatiramer acetate currently considered first-line therapies.<sup>1</sup> Many newer agents are also being introduced, including tyrosine kinase inhibitors.<sup>2,3</sup>

Unfortunately, recent evidence has emerged regarding the potential pregnancy-related adverse

effects of DMDs.<sup>4</sup> In general, DMD therapy is discontinued during pregnancy, although the actual risk of adverse effects occurring due to IFN- $\beta$  and glatiramer acetate appears to be low.<sup>5</sup> This report describes a pregnant woman who took IFN- $\beta$  throughout her first trimester and subsequently developed severe placental complications.

## Case Report

A 30-year-old *gravida 2 para 1* woman presented to the Tawam Hospital, Al Ain, United Arab Emirates, in 2013. She had been diagnosed with relapsing-remitting MS five years previously, after she had developed unilateral optic neuritis with frequent relapses. These symptoms had progressed two years later to epilepsy and left-sided haemiplegia and her MS was re-classified as secondary progressive MS. She was prescribed IFN- $\beta$  1a at a dose of 30  $\mu$ g weekly as a lifelong

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**Figure 1:** Prenatal ultrasonography of a pregnant woman with multiple sclerosis showing a fetus with a mildly dilated echogenic bowel.

prophylactic therapy as well as levetiracetam at a dose of 750 mg twice daily to control her epilepsy. In 2013, she conceived spontaneously; however, the medication was discontinued only at 13 gestational weeks after her first visit to an obstetrician. Levetiracetam was continued throughout her pregnancy.

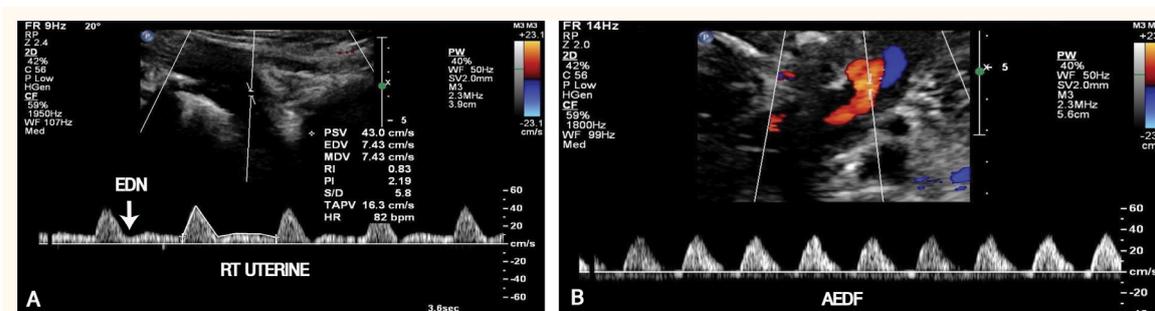
During her pregnancy, the patient remained stable; however, a fetal ultrasound at 22 gestational weeks indicated that all fetal growth parameters had decreased. Severe early-onset fetal growth restriction (FGR) was diagnosed. The results of a detailed anatomic survey, karyotyping by amniocentesis and a virology screening test were normal. However, prenatal ultrasonography revealed that the fetus had an echogenic mildly dilated bowel [Figure 1], most probably due to *ischaemia*. A uterine artery Doppler ultrasound revealed high-resistance flow with early diastolic notching [Figure 2A] and an umbilical artery Doppler ultrasound showed absent end-diastolic flow [Figure 2B]. Additionally, the patient suffered from oligohydramnios. These findings were suggestive of placental insufficiency as the cause for early-onset FGR. The patient was subsequently monitored with a series of biophysical tests.

At 30 gestational weeks, the patient developed

severe pre-eclampsia that was further complicated by HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome. As a result, an emergency Caesarean section was performed and the patient was given full high-intensive care to manage the pre-eclampsia, including magnesium sulphate infusions, serial monitoring of vitals and renal and respiratory function tests. Post-delivery, the patient had an uneventful recovery and was discharged eight days after the Caesarean section in stable condition with the advice to continue IFN- $\beta$  as lifelong prophylactic therapy. In this case, the placenta was not sent for histopathology examination; it is recommended to do so in future cases. At birth, the female baby weighed 980 g and was admitted to the Neonatal Unit of Tawam Hospital. A physical examination did not reveal any malformations or abnormalities. The neonate required a postnatal course of surfactant for respiratory distress. She also required total parenteral nutrition initially but subsequently tolerated enteral feeds. She was discharged at the age of two months.

## Discussion

There are four clinical types of MS, including relapsing-remitting MS, secondary progressive MS, primary progressive MS and progressive-relapsing MS. Generally, DMDs are recommended for patients who suffer from relapsing forms of MS, such as relapsing-remitting MS or secondary progressive MS with exacerbations; the prescription criteria include abnormal neurological examinations, several MS attacks and a high burden of disease as assessed by magnetic resonance imaging of the brain.<sup>1</sup> The patient in the current case was an ideal candidate for DMDs as she was first diagnosed with relapsing-remitting MS, which then progressed to secondary progressive MS with permanent neurological complications. Hence, she was on lifelong prophylactic therapy with IFN- $\beta$  1a.



**Figure 2A & B:** Doppler ultrasonography of (A) the uterine arteries revealing high-resistance flow with early diastolic notching (arrow) and (B) the umbilical artery showing absent end-diastolic flow in a pregnant woman with multiple sclerosis.

EDN = early diastolic notching; RT = right; AEDF = absent end-diastolic flow.

In the current case, the patient was prescribed levetiracetam monotherapy to control her epilepsy during pregnancy. With levetiracetam, the risk of major congenital malformations is comparable with that of the non-epileptic population, indicating the relative safety of the drug.<sup>6</sup> On the other hand, a systematic review reported that IFN- $\beta$  exposure was associated with lower mean birth weight, shorter mean birth length and preterm birth, although the drug was not associated with increased risk of low birth weight infants (<2,500 g), Caesarean section delivery, congenital anomalies or spontaneous abortion.<sup>4</sup> Due to the limited data regarding the effect of DMDs on pregnancy outcomes, women are advised to stop taking the drug either three months or at least one month prior to conception.<sup>7,8</sup> Close follow-up is recommended for patients who continue taking DMDs during their pregnancies in order to assess and prevent the development of any fetal or maternal complications. Women with MS should be given more education regarding the risks of DMDs in pregnancy.

Extra-villous trophoblast (EVT) cells are fetal cells that invade the mother's uterus, where they transform the spiral arteries into large vessels capable of conducting sufficient blood to the placenta.<sup>9</sup> Early trophoblast invasion is important for placental function and the extent of arterial transformation by the trophoblasts affects successful reproductive outcomes.<sup>9</sup> Severe early-onset FGR overlapping with severe pre-eclampsia, as in the present case, is mainly associated with features of impaired maternal uteroplacental perfusion secondary to defective EVT invasion, which results in insufficient blood supply to the placenta.<sup>10,11</sup> Placental histopathological findings generally reflect abnormal uteroplacental flow with secondary chronic fetal vasoconstriction and distal villous changes.<sup>11,12</sup> Trophoblast invasion is controlled by the uterine natural killer cells (uNK cells), the most common uterine leukocyte.<sup>9,13</sup>

The efficacy of IFN- $\beta$  in patients with MS is due to its immunomodulatory properties; the drug downregulates major histocompatibility molecules on antigen-presenting cells, inhibits proinflammatory cytokine levels, increases regulatory cytokine levels, inhibits T cell proliferation and limits the trafficking of inflammatory cells in the nervous system.<sup>1</sup> These properties evidently oppose the effects of uNK cells.<sup>9,13</sup> The patient in the current case took IFN- $\beta$  until the 13<sup>th</sup> week of her pregnancy, which is when EVT invasion and placental development occurs.<sup>9</sup> However, further research is required to determine whether DMDs are related to placental insufficiency. Studies using experimental animal models are recommended to assess the relationship between IFN- $\beta$  and EVT invasion or placental development.

## Conclusion

This case describes severe placental complications in a pregnant woman with MS who continued taking IFN- $\beta$  during her first trimester. The continuation of this DMD well into the period of full placental development may have contributed to the development of early-onset FGR and pre-eclampsia in this patient. However, further research into this issue is required to determine whether these factors are related. It is advisable that women who continue taking DMDs during their pregnancies should be followed-up closely to assess and prevent the development of fetal and maternal complications.

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