EXPERT OPINION

Glatiramer acetate to treat multiple sclerosis during pregnancy and lactation: a safety evaluation

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Introduction: Multiple sclerosis (MS) is a disease that mainly affects young adults who are of reproductive age. MS can lead to severe disability and is associated with worse prognosis in untreated patients. Although MS is not negatively affected by pregnancy itself, it may be a high-risk decision to leave a woman without treatment because she may get pregnant.
Areas covered: This paper reviews the literature on pregnancies where the mother was exposed to glatiramer acetate. Few data are available on paternal exposure, but this does not seem to pose a problem due to the pharmacological characteristics of the drug. Only a limited amount of data from individual groups in the world is available in the literature.
Expert opinion: TEVA Pharmaceuticals would need to open the database on pregnancy exposure to glatiramer acetate to allow for proper conclusions. Glatiramer acetate is a drug of low risk in pregnancy (category B in the FDA classification) and may be a safe option for the treatment of women of fertile age with MS.

Keywords: glatiramer acetate, lactation, malformations, pregnancy, safety

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1. Introduction

1.1 Multiple sclerosis and pregnancy

Multiple sclerosis (MS) is a chronic demyelinating and degenerative disease of the central nervous system that is most frequently manifested in early adulthood. MS is most often observed in women between their second and fourth decades of life. Thus, it is no wonder that the subject of pregnancy among patients with MS has received so much attention from researchers and clinicians over the years. As early as 1986, Birk and Rudick [1] already stated that except for the high risk of relapses in the postnatal period, no other signs of instability of MS could be observed in relation to pregnancy. The classic work of Confavreux *et al*. in 1998 [2] established, in a prospective multicenter study, that the rate of relapses significantly decreases during pregnancy and increases in the postnatal period. Pregnancy probably ameliorates the short-term course of MS in terms of relapse rate and progression to disability [3]. With this information at hand, we have moved from a time when pregnancy was discouraged to an era when women with MS should not be discouraged from starting or continuing to have children. With this leap forward, other questions have become part of daily practice: Should women be left without disease-modifying drugs (DMDs) because they may become pregnant? Are DMDs hazardous for the gestation and/or the baby? What if a woman becomes pregnant while taking DMDs? As the rate of women without any relapses during pregnancy is not zero, what can we do with women who have relapses or present more aggressive disease?

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Box 1. Drug summary.

Drug name	Glatiramer acetate – Copaxone®
Phase	IV
Indication	Relapsing-remitting multiple sclerosis
Pharmacology description	polypeptide mixture synthesized by copolymerization of four naturally occurring amino acids (glutamic acid, lysine, alanine and tyrosine).
Route of administration	Subcutaneous
Chemical structure	(Glu, Ala, Lys, Tyr)x•$X$$CH_3COOH$ ($C_5H_9NO_4$•$C_3H_7NO_2$•$C_6H_{14}N_2O_2$•$C_9H_{11}NO_3$)x•$X$$C_2H_4O_2$ CAS - 147245-92-9
Pivotal trial(s)	[26,27]

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What if a man with MS taking DMDs fathers a child? And last but not the least, could DMDs decrease the risk of postnatal relapses?

1.2 Recommendations and guidelines

It is remarkable that most of the literature on the subject of treatment of MS during pregnancy consists of reviews and guidelines and not original work. For many years, neurologists and obstetricians were extremely concerned about exposure to DMDs during conception and early pregnancy. The rates of pregnancy termination were high and an era of recommendation for women to stop all DMD treatment if they were planning to become pregnant started. This recommendation could be found in many guidelines, and it was stated that a period of a few months should be observed between stopping the DMD and conceiving. However, this attitude clashed with the concepts that MS must be treated early and energetically [4] and that there is no such thing as benign MS [5]. As interrupting the treatment of MS may lead to rapid reactivation of the disease, why should women who want to have a child run this risk [6]? There is no guarantee that the woman will conceive in only a month or two, and well-controlled disease may easily become out of control because of sudden interruption of DMD treatment.

To worsen the situation, many women (irrespective of whether they have MS) do not plan their pregnancies in such an organized manner. What if a woman becomes pregnant while taking DMDs? Should the gestation be terminated? Should the woman interrupt the MS treatment even if her disease was not under control and hope that the pregnancy will bring the relapse rate to zero? How far into the pregnancy is it safe to take DMDs? Several papers have reported on the relatively safety of DMD exposure during pregnancy, particularly regarding interferon-β and glatiramer acetate, which have been in use for circa 20 years [7,8].

Another question has arisen over the last few years. If a woman is being treated for MS during pregnancy, does her risk of postnatal relapses decrease? Exposure to DMDs during pregnancy seems to be protective against postpartum relapse [8,9]. Use of natalizumab during the third trimester of pregnancy may also alter the postnatal relapse rate [10]. These findings highlight the importance of considering DMD exposure as a potential modifier of postpartum disease activity when counseling women with MS who are planning to become pregnant.

1.3 Glatiramer acetate

Glatiramer acetate is a polypeptide mixture synthesized by copolymerization of four naturally occurring amino acids (glutamic acid, lysine, alanine and tyrosine). A drug summary box is presented as **Box 1**. The drug was originally developed to resemble myelin basic protein, with the aim of inducing demyelinating responses in animal models of MS. Unexpectedly, the animal disease was suppressed by the mixture of polypeptides [11] and the drug was then put into clinical trials, with success [12]. A couple of decades later, glatiramer acetate has become one of the most prescribed drugs for MS and it is still considered to be first-line therapy worldwide.

The mechanism of action of glatiramer acetate is complex and possibly dual: at the same time as it regulates the inflammatory response of lymphocytes, it may also have a parallel neuroprotective effect via brain-derived neurotrophic factor [13].

1.4 Glatiramer acetate and pregnancy

Out of all the drugs used for the treatment of MS, only glatiramer acetate is considered to present low risk for use during pregnancy. Glatiramer acetate is classified as category B by the FDA [14], meaning that animal reproduction studies have failed to demonstrate any risk to the fetus, but there are no adequate well-controlled studies among pregnant women.

For a long time, there has been criticism of this classification as the FDA system requires availability of controlled studies on pregnant women [15]. For a drug to be assigned to category A, high-standard studies failing to demonstrate a risk to the fetus are needed. Consequently, the majority of drugs are classified as category C by the FDA, interpreted as 'risk cannot be ruled out'. Thus, other drugs currently categorized as C on this FDA list (interferon-β, natalizumab,

Table 1. Reports on the outcomes of pregnancies where the mothers had been exposed to glatiramer acetate (GA).

	Author	Year	Country	Number of pregnancies exposed to GA	Duration of exposure	Exposure during breastfeeding	Complications due to exposure
Maternal exposure	Coyle *et al.* [14]	2003	USA	345	Variable	Not reported	13% miscarriages, six birth defects: cleft lip, finger abnormality, anencephaly, cardiomyopathy, urethrostenosis, adrenal cyst
	Fragoso *et al.* [28]	2009	Brazil	15	Variable	Yes	None
	Weber-Schoendorfer & Schaefer [29]	2009	Germany	31	Variable (average 6.9 weeks)	Not reported	Two birth defects: club feet and atrioventricular canal
	Fernandez Liguori *et al.* [30]	2009	Argentina	3	4 weeks	No	One birth defect: urethrostenosis
	Slaminen *et al.* [31]	2010	UK	10	Throughout pregnancy	Not reported	One miscarriage
	Fragoso *et al.* [32]	2010	Brazil	11	Throughout pregnancy	Yes	None
	Hellwig & Gold [33]	2011	Germany	3	Throughout pregnancy	Yes	None
	Hellwig *et al.* [34]	2012	Germany	41	Variable (average 6 weeks)	No	Two birth defects: abnormality of urinary bladder valves and hip dysplasia
	Lu *et al.* [35]	2012	Canada	6	4 – 8 weeks	No	None
	Giannini *et al.* [36]	2012	Italy	17	4 weeks	No	One miscarriage
	Fragoso *et al.* [37]	2013	Brazil, UK, Mexico, Argentina	37	8 – 40 weeks	Yes	Two miscarriages, three terminations, one neonatal death, one bone malformation
	Fragoso *et al.* [8]	2013	Brazil	39	2 – 40 weeks	Yes	Long-term assessment in the life of the infant: nothing relevant
	Vanya *et al.* [38]	2014	Hungary	15	Variable	Not reported	Four miscarriages, two neonatal deaths
Paternal exposure	Pecori *et al.* [39]	2014	Italy	6	Conception	-	None

fingolimod, fumarate, alemtuzumab and corticosteroids) may after all be relatively safe. The exception to this statement is teriflunomide, recently approved for the treatment of MS and classified as category X (fetal toxicity). If the FDA category list for safety in pregnancy is to be followed, only glatiramer acetate really poses minimal risk to the fetus. It is important to highlight that other countries have other ways of classifying the safety of drug exposure during pregnancy, but in all of them glatiramer acetate rates as low risk.

1.5 Published data on glatiramer acetate and pregnancy

There is no published database from TEVA Pharmaceuticals, which produces and commercializes glatiramer acetate (Copaxone®). None of the present author's attempts to obtain information directly from TEVA relating to its database on exposure of pregnant women to glatiramer acetate yielded any results. Thus, although thousands of cases of exposure may be registered in their database, this is not open to researchers. The only study acknowledged to have been supported by TEVA and its database was the postmarketing surveillance study by Dr. P. Coyle, which was presented in 2003 [16].

The data available on pregnancies with exposure to glatiramer acetate are summarized in **Table 1**. Only the results from original research reporting on pregnancies exposed to glatiramer acetate have been taken into consideration. Some of these pregnancies may be the same ones reported in more than one paper, and thus the data may have overlapped. In cases in which the exposure to glatiramer acetate was unclear [17,18], the information was not included in the table. It is perhaps reassuring to observe that only just over

500 pregnancies with glatiramer acetate exposure have been reported. More than half of these pregnancies were reported in 2003, in a postmarketing assessment [16], whereas circa 200 are from individual groups reporting on their observations. Few and unspecific birth defects were reported in these cases, and it might be assumed that malformations would have led to publication. It would also be expected that TEVA Pharmaceuticals would have issued a warning in case of a pattern of malformations. The fact that so few papers have reported on glatiramer acetate and pregnancy is somewhat reassuring regarding the low risk posed by this drug. There is only one paper that assessed the offspring over the long term (> 1 year) [8]. No particular unfavorable outcomes to offspring came from maternal exposure to glatiramer acetate: not even allergies, which might have been expected if the immunological system of the child had been affected.

1.6 Data on glatiramer acetate and breast feeding

There are very little data on breast feeding while any DMD is being taken. Although details of obstetric and neonatal complications appear in all the papers dealing with DMD exposure during pregnancy, virtually nothing can be found on exposure during breast feeding. At the moment, it seems that women with MS might have to make a difficult choice between not restarting their DMD while breast feeding or restarting therapy and not breast feeding [19,20]. There are potential beneficial effects from breast feeding regarding the course of MS [19-21], and current medical advice, though not evidence-based, contraindicates breast feeding while taking DMDs [22]. Among doctors who prescribe DMDs while breast feeding, glatiramer acetate is the drug of choice [23].

However, although no specific data about glatiramer in breast milk can be found, information from the manufacturer indicates that after subcutaneous injection, glatiramer undergoes rapid degradation to amino acids and small peptides. Glatiramer acetate cannot be detected in the plasma, urine or feces [24]. Furthermore, any glatiramer acetate that might reach the breast milk would probably be destroyed in the infant's gastrointestinal tract and would not be absorbed. The limited information available indicates that maternal use of glatiramer does not cause any adverse effects in breastfed infants [25].

2. Conclusion

Glatiramer acetate may be a good therapeutic option for women of fertile age who have MS. Whether a pregnancy is planned or accidental, exposure to glatiramer acetate does not seem to negatively influence the obstetric and neonatal outcomes. Use of glatiramer acetate throughout pregnancy may control relapses during and after the gestational period. There is no sensible reason to contraindicate breast feeding for a woman who takes glatiramer acetate.

3. Expert opinion

MS is a disease of the central nervous system that can progress with severe disability. As MS affects young adults, and predominantly women, the safety of drugs during pregnancy is an important point to consider. Although no drug exposure at all during conception and gestation is the ideal situation, women with MS cannot be left without treatment for a potentially disabling disease. Glatiramer acetate may be a good alternative for the patient to be under treatment while attempting to conceive. Glatiramer acetate could also be a good option for the treatment of women of fertile age who may become pregnant without planning it. The major advantage of glatiramer acetate over other drugs is its 'B' classification in the FDA categories for drugs during pregnancy. This was achieved through the favorable pharmacokinetics of the drug and the lack of teratogenic evidence. There are few data published on maternal and offspring complications relating to glatiramer acetate, and no hazardous pattern can be established between the drug and the outcomes.

Although no physician would have approved of pregnancy for women with MS half a century ago, and many still believe that women with potential childbearing capacity should not be treated, attitudes may change in the near future. MS needs to be treated with rigor from the outset of its manifestations and the treatment must not be interrupted without a very sound motive. Even if the physician and the patient decide to stop treatment during pregnancy, glatiramer acetate could be used until conception. In fact, it can even be used throughout pregnancy if deemed necessary.

It is likely that 5 years from now glatiramer acetate will be less used for the treatment of MS worldwide. Daily injections of Copaxone (or nearly daily injections with its new formulation) may prove less attractive in a world where many oral therapies are becoming available to treat MS. On the other hand, the relatively safe profile of glatiramer acetate for women of fertile age who are planning a pregnancy (or who may become pregnant) may guarantee a place for this drug in the market for a very long time.

My personal recommendation is that TEVA Pharmaceuticals should open their database on reports of pregnancy in women using glatiramer acetate in order to provide sufficient data on exposures for neurologists and obstetricians to feel safer in prescribing this drug.

Declaration of interest

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. YD Fragoso has no conflicts of interest to declare.

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