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Clinical short communication

Effect of pregnancy loss on MS disease activity

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ABSTRACT

Objective: To evaluate the effect of pregnancy loss (PL) on MS disease activity.
Methods: Eleven women with first-trimester PLs were identified through a reproductive questionnaire. MS activity (MRI lesions and/or clinical relapses) was compared for the 12 months before conception and after PL.
Results: There was MS activity in 7/11 participants after, compared with 3/11 before PL (McNemar's test, $p = .29$), including MRI activity in 7/11 after, compared with 2/11 before PL (McNemar's test, $p = .13$).
Conclusion: Larger studies are needed to confirm this observed trend of increased MS activity following PL.

1. Introduction

Multiple Sclerosis (MS), an immune mediated disease of the central nervous system (CNS) that often presents during the childbearing years. Since the landmark 1998 Pregnancy in Multiple Sclerosis (PRIMS) study, the decreased relapse risk during later pregnancy followed by a rebound risk in the first 3 months postpartum is well-recognized [1]. In contrast, little is known about the course of disease during incomplete pregnancies, despite the fact that 15–20% of all pregnancies end in miscarriage (80% of which occur in the first trimester [2]).

In this series, we explored inflammatory activity (clinical and radiographic on MRI) in a prospectively followed cohort of women who experienced a first-trimester pregnancy loss (PL).

2. Methods

A reproductive questionnaire was deployed to all adult women with MS or clinically isolated syndrome who were actively followed as part of a single-center prospective observational study (CLIMB), as previously described. From 724 respondents (60% response rate), all pregnancies resulting in PL (whether from miscarriage or therapeutic abortion) during respondents' period of observation in CLIMB were identified and validated against the electronic medical record when available. Outcomes were recorded for the 12 months (12 M) before conception and after PL: [1] MRI activity as defined by either new T2 or Gadolinium-enhancing (Gd +) lesions and [2] documented clinical relapse.

3. Results

From the 724 survey responses, 517 subjects reported ever being pregnant but only 98 of these pregnancies occurred after the diagnosis of MS and during the CLIMB observation period. Of these 98 pregnancies, 21 ended in PL occurring in 19 participants. From these, 8 participants were excluded due to either [1] incomplete relapse or MRI data ($N = 5$), or [2] conception within the 3 M following a PL that eventually resulted in a live birth ($N = 3$). The remaining 11 participants with PLs, who had complete relapse and MRI data 12 M preconception and 12 M after PL, were included.

In this group, average (SD) age at PL was 35.5 (3.1) years and disease duration was 6.6 (3.7) years. All the pregnancies ended in spontaneous abortion during the first trimester. Nine out of 11 participants were treated with a DMT prior to pregnancy, including: interferon [2], natalizumab, fingolimod, daclizumab, rituximab and mycophenolate mofetil; all discontinued DMT prior to conception except subject 3, who discontinued her interferon therapy two weeks after conceiving. The time course in which participants discontinued and resumed therapy is further outlined in Table 1. Of note, some of this information was unavailable in the electronic medical record. Within the 12 M after PL, 7 participants resumed DMT; 4 remained off DMT (3 planned another conception).

During the 12 M before pregnancy, only one participant had a documented clinical relapse without MRI activity after fingolimod discontinuation. This participant had discontinued fingolimod 5 months prior to conceiving, and her relapse occurred during that 5-month

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Table 1
Relapse and MRI activity before and after 11 pregnancies resulting in spontaneous abortion within the first trimester.

Patient	Age	Disease duration (years)†	DMT prior to pregnancy	DMT discontinuation prior to pregnancy	Relapse within 12M prior to pregnancy	MRI activity within 12M prior to pregnancy	Duration of pregnancy	Relapse within 3M after pregnancy loss	Relapse within 12M after pregnancy loss	MRI Activity within 12M after pregnancy loss	Received IV steroids within 12M after pregnancy loss	Resumption of DMT after PL
1	31	5	Natalizumab	1 mo	0	No	< 3 mo	0	0	Yes, New Gd+	Yes, after MRI	Natalizumab, (5 mo)
2	38	16	IFN-β1b	Over 1 year	0	No	< 3 mo	1	0	Yes, New T2	No	No
3	32	7	IFN-β1a	2 wks after conception	0	No	< 3 mo	0	1	Yes, New T2	Yes, after relapse	IFN-β1a (several weeks)
4	38	6	Fingolimod	5 mo	1	No	< 3 mo	0	0	No	No	No
5	39	7	Daclizumab	N/A	0	No	< 3 mo	0	0	Yes. New T2	No	Daclizumab (6-12 mo)
6	38	7	Rituximab	N/A	0	No	< 3 mo	0	0	Stable	No	Rituximab (6-12 mo)
7	34	1	None	N/A	0	Yes, New T2	< 3 mo	0	0	Yes, New Gd+	No	N/A
8	33	4	IFN-β1a	N/A	0	Yes, New T2	< 3 mo	0	0	No	No	No
*9	32	6	Mycophenolate mofetil Stopped 3 months before 1st preg. Stopped Aug '08, conceived Oct '08	3 mo before 1st pregnancy	0	No	< 3 mo	0	1	Yes, new Gd+	Yes, after relapse	Mycophenolate mofetil, (6 mo after PL, after MRI with new Gd+. Off tx for 39 weeks)
10	37	5	None	N/A	0	No	< 3 mo	1	0	Yes, New Gd+	Suggested but pt declined	No
11	38	8	Rituximab	6 mo	0	No	< 3 mo	0	0	No	No	Rituximab (3 mo)

N/A = data not available
Mo = months
† Rounded to nearest year
* Two consecutive pregnancy losses within a 5-month period

period. Two other participants developed asymptomatic new T2 lesions on MRI, and none developed Gd + −lesions. In contrast, during the 12 M after PL, 7 of the 11 participants had MRI activity (either new T2 or Gd + lesions) including one participant (#7) with pre-partum MRI activity. Of note, subject 7 was not on any DMT pre or post PL. The MRI activity corresponded to clinical relapses in 4 participants. Three participants received intravenous methylprednisolone (2 with clinical and MRI activity, and one with MRI activity alone); one additional participant declined (#10). Overall, in the 12 M after PL, 7/11 (64%) of women had any MS activity (relapse and/or MRI) compared with 3/11 (27%) in the 12 M before (McNemar's test, $p = .29$), and 7/11 (64%) had MRI activity compared with 2/11 (18%) in the 12 M before (McNemar's test, $p = .13$).

4. Discussion

In this case series of prospectively collected disease activity in 11 women with first trimester PLs, we observed an apparent increase in both MRI activity and clinical relapse after PL.

Several hypotheses can be considered for this observation of increased inflammatory disease activity after a PL. First, as these women discontinued their DMTs prior to conceiving, they could have experienced either recurrence of their baseline MS activity, or rebound disease activity in the case of discontinuation of fingolimod and natalizumab (participant #1) [3]. However, it is worth noting that the observed relapses occurred in patients who were either on interferon therapy ($n = 2$), mycophenolate mofetil ($n = 1$) or not on treatment (n = 1) so that rebound activity after DMT discontinuation clearly cannot entirely explain the clinical relapses observed. Still, one participant, who was noted to have new Gd + lesions on an MRI performed 5 months post PL, had been on natalizumab therapy prior to conception. Second, a sharp rise and then withdrawal of hormones during an incomplete pregnancy without the accompanying sustained protective immune changes seen in 2nd and 3rd trimesters could be contributory [4]. The protective effect of pregnancy has been grossly attributed to a Th1 to Th2 immune shift [5]. In the later stages of pregnancy, sustained rises in estrogens (β-estradiol and estriol) and progesterone likely promote Th1 to Th2 shift which result in downstream inhibition of Th1-mediated proinflammatory cytokines such as TNF-α and IFN-γ [4,5]. Yet, after a pregnancy is lost, there is a sharp and persistent decrease in hormonal levels, including follicle stimulating hormone (FSH) and luteinizing hormone (LH) and consequently lower estrogen and progesterone levels [6,7]. This abrupt state of hormone withdrawal could result in increased synthesis of proinflammatory cytokines, as is seen postpartum after completed pregnancies [8]. A final mechanism could be stress. Since Charcot, stress has been putatively linked to relapse risk [9] and activity on MRI. The loss of a desired pregnancy is often associated with grief and emotional stress in the general population [10]. In women with MS, PL could also be a significant stressor potentially increasing relapse risk.

It is unlikely that these observed pregnancy losses were due to the DMTs themselves. All participants discontinued their DMT use months in advance with the exception of subject 3, who discontinued interferon therapy two weeks after conception. Fingolimod does cross the placenta, and has been associated with both teratogenicity and embryolethality in animal studies and a higher rate of spontaneous abortions and malformations in humans [11]. However, in this cohort, the only participant on fingolimod (#4) had discontinued therapy 5 months prior to conception, so this was unlikely a contributing factor in her pregnancy loss.

Limitations of this case series include the small size, the potential for recall and other forms of bias in patient-reported PL ascertainment, and the potential for missing information in the electronic medical record given that some participants did not receive obstetric and neurologic care within the same health care system. There is also a lack of information on possible confounders, such as the causes for PLs, including obstetric, infectious or traumatic events. Furthermore, because at the time MRIs were not routinely obtained with 3 M of delivery or PL, we looked at MRI activity within 12 M of PL; it is possible that MRIs obtained sooner after PL might have revealed additional signs of activity (Gd + lesions).

The natural course of a completed pregnancy in MS has been well documented, but there is a lack of data on MS activity after PL, a very common occurrence. Despite the low number of subjects, our case series suggests a trend for increased MS activity after PL. Prospective studies with larger sample sizes are needed to better understand the effects of PL on MS disease activity, but this current case series provides some preliminary clues.

Conflicts of interest

The authors declare there are no conflicts of interest.

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