Pregnancy outcomes during treatment with interferon beta-1a in patients with multiple sclerosis

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Abstract—*Background:* Although patients with multiple sclerosis (MS) are advised to stop interferon (IFN) beta-1a therapy before becoming pregnant, some patients become pregnant while on treatment. *Methods:* We examined individual patient data from eight clinical trials with IFNβ-1a. *Results:* Of 3,361 women in the studies, 69 pregnancies were reported, of which 41 were patients receiving (or who had stopped receiving within 2 weeks prior to conception) IFNβ-1a (in utero exposure group), 22 were patients who discontinued IFNβ-1a treatment more than 2 weeks before conception (previous exposure group), and six were patients receiving placebo. The 41 in utero exposure pregnancies resulted in 20 healthy full-term infants, one healthy premature infant, nine induced abortions, eight spontaneous abortions, one fetal death, and one congenital anomaly (hydrocephalus). One patient was lost to follow-up. The 22 previous exposure pregnancies resulted in 20 full-term healthy infants, one healthy premature infant, and one birth-related congenital anomaly (Erb palsy) *Conclusions:* The majority (21/31) of pregnancies that had the potential to go to full term produced healthy infants. The rate of spontaneous abortion was higher, but not significantly so, in the in utero exposure group compared to general population estimates. Until more exposure data become available, patients remain advised to stop IFNβ therapy before becoming pregnant.

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Therapy with IFNβ-1a has demonstrated benefit in patients with relapsing-remitting multiple sclerosis (RRMS).[1-3] MS generally has its onset in women during their childbearing years[4] but there is no evidence that MS increases the risk of spontaneous abortion or congenital defects.[5] Limited data in primates suggest the possibility that IFNβ administration may be an abortifacient. Based on this and the lack of data regarding the effects of IFNβ therapy during pregnancy, women are advised to discontinue IFN therapy before becoming pregnant. We reviewed the pregnancy outcomes of women enrolled in clinical trials of IFNβ-1a in MS.

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Methods. *Patients.* We reviewed individual patient data obtained from eight clinical trials with IFNβ-1a conducted between 1994 and 2003: five studies of patients with RRMS,[1,2,6-10] two of patients with secondary progressive MS (SPMS),[11-12] and one of patients after a first episode of suspected demyelinating disease (table 1).[13]

Drug-dosing regimens. Five of the trials were placebo-controlled,[1,7,11-13] with extension phases of variable duration.[2] Two trials used active comparators[6,8] and one was a comparison between two delivery systems, with all patients on active drug.[9] IFNβ-1a was administered either subcutaneously (SC) to 4,381 patients (Rebif, Serono International, Geneva, Switzerland) or intramuscularly to 337 patients (Avonex, Biogen Idec, Cambridge, MA) (table 1). Doses ranged from 22 μg QW to 44 μg TIW and the duration of treatment ranged from 3 months[9] to 7.5 years.[10]

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Table 1 *Summary of the controlled clinical trials with IFNβ-1a*

Study	Indication	Patients who received treatment, M/F	Treatment around the time of conception*	Pregnancies, n
PRISMS[1,2,10] (1994–2003)	RRMS	171/389	22 μg TIW	24
			44 μg TIW	16
			Placebo	3
EVIDENCE[6] (1999–2002)	RRMS	171/505	44 μg TIW	7
			30 μg QW (IM)	2
OWIMS[7] (1995–1998)	RRMS	80/213	22 μg QW	3
			44 μg QW	2
			Placebo	0
Mikol et al.[9] (2001–2002)	RRMS	421/1404	44 μg TIW	3
Pozzilli et al.[8] (1994–1996)	RRMS	21/47	11 μg TIW	0
			33 μg TIW	1
SPECTRIMS[1] (1994–2001)	SPMS	229/389	22 μg TIW	1
			44 μg TIW	3
			Placebo	1
Nordic SPMS study[12] (1995–2001)	SPMS	147/217	22 μg QW	0
			Placebo	2
ETOMS[13] (1995–2002)	Patients at high risk of developing MS	112/197	22 μg QW	1
			Placebo	0

* Subcutaneous unless noted.

PRISMS = Prevention of Relapses and Disability by Interferon Beta-1a Subcutaneously in Multiple Sclerosis; RRMS = relapsing–remitting multiple sclerosis; EVIDENCE = Evidence of Interferon Dose Response European and North American Comparative Efficacy Study; OWIMS = Once Weekly Interferon for Multiple Sclerosis; SPECTRIMS = Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon Beta-1a in Multiple Sclerosis; SPMS = secondary progressive multiple sclerosis; ETOMS = Early Treatment of Multiple Sclerosis; IFN = interferon.

Pregnancy data. Individual narratives of pregnancies occurring during studies chronicled the duration of in utero exposure to IFNβ-1a, treatment regimen, and the outcome of the pregnancy. In utero exposure was calculated from the date of conception (estimated date of delivery minus 38 weeks). If this date was missing, the date of conception was calculated using either the date of the last menstrual period (+14 days), ultrasound data, or clinical examination. A two-sided, one-sample binomial test was used to test whether the observed rates of spontaneous abortion and fetal death in the in utero exposure group were different from the rate estimated for spontaneous abortion (15% to 20%) and fetal death (0.65% to 0.7%) in the general population. Where percentages are calculated to describe pregnancy outcomes in the in utero exposure and previous exposure groups, denominators used represent either "known" outcomes (total number of pregnancies minus one case lost to follow-up, n = 62), "potential to go full-term" outcomes (total number of pregnancies minus lost to follow-up and elective abortions, n = 53), or "live birth" outcomes (total number of pregnancies minus lost to follow-up, elective abortions, and pregnancy losses, n = 44).

Results. *Demographics.* Of the clinical trial patients, 71% (3,361/4,713) were women with a mean baseline age of 39.5 years (range 17 to 74 years). A total of 69 pregnancies were reported, 41 of which occurred in patients who were receiving IFNβ-1a at the time of conception or had discontinued IFNβ-1a within 2 weeks prior to conception (in utero exposure group). Twenty-two pregnancies were reported in patients who had discontinued active therapy more than 2 weeks prior to conception (previous exposure group) and six pregnancies occurred in patients receiving placebo (placebo group). There were fewer individuals randomized to placebo and placebo exposure time was less than IFN exposure because, during the extension phases of the studies, placebo patients converted to active therapy. The means of the maternal ages at conception for the three groups were similar (in utero exposure: 29.8, range 19 to 39 years; previous exposure: 30.3, range 25 to 38 years; placebo: 31.7, range 27 to 35 years). Of the 69 pregnancies, 61 occurred in patients with RRMS, seven in patients with SPMS, and one in a patient diagnosed as being at risk of developing MS (table 1).

Pregnancy outcomes. Results of pregnancy outcomes are presented in table 2.

In utero exposure group. Forty-one women were exposed to IFNβ-1a during (n = 38) or immediately before (n = 3) conception. These pregnancies resulted in 22 live births (55% of 40 cases with known outcomes and 71% of 31 that could potentially go full term). Of these, 20 resulted in full-term healthy infants, of which three had mild complications during delivery (fetal distress and bradycardia, partial pulmonary atelectasis, and mild jaundice). Of the two remaining live births, one was premature and one had a congenital anomaly. The premature infant was born to a 27-year-old woman who had been receiving IFNβ-1a, 22 μg TIW, for 27 months and discontinued therapy approximately 1 week prior to conception. Placental separation was detected at 34 weeks' gestation and a healthy baby was delivered by Cesarean section. The congenital anomaly was a case of hydrocephalus requiring surgery at 13 months of age, born to a woman who took IFNβ-1a, 22 μg TIW, throughout pregnancy.

Table 2 *Pregnancies reported in clinical trials (1994–2003)*

	In utero exposure*	Previous exposure†	Any IFNβ-1a treatment	Placebo	Total
Live births					
Full-term healthy	20	20	40	2	42
Premature healthy	1	1	2	0	2
Full-term abnormality	1	1‡	2	1	3
Total live births	22	22	44	3	47
Pregnancy losses					
Spontaneous abortions	8	0	8	0	8
Fetal death	1	0	1	0	1
Total pregnancy losses	9	0	9	0	9
Pregnancies with potential to go full term	31	22	53	3	56
Induced abortions	9	0	9	3	12
Pregnancies with known outcome	40	22	62	6	68
Lost to follow-up	1	0	1	0	1
Total pregnancies	41	22	63	6	69

* On IFNβ-1a at conception or discontinued in the 2 weeks preceding conception.
† Discontinued IFNβ-1a more than 2 weeks prior to conception.
‡ Birth-related congenital anomaly (Erb palsy).

IFNβ-1a in utero exposure in the 20 women delivering full-term healthy infants was 1 to 4 weeks (n = 16), 5 to 8 weeks (n = 3), and 16 weeks (n = 1). Ten women received IFNβ-1a at a dose of 44 μg TIW, eight received 22 μg TIW, one received 30 μg QW, and one received 22 μg QW. The course of each live birth in the in utero exposure group is illustrated in the figure.

Nine women (22.5% of 40 exposed pregnancies with known outcomes) elected to terminate pregnancy, on average 6.2 weeks (median 7.0, range 2 to 12 weeks) after conception with a mean in utero exposure of 4.2 weeks (median 4.0, range 2 to 10 weeks).

Another nine women in the in utero exposure group experienced pregnancy loss (table 3) yielding a pregnancy loss rate of 29% (9/31). Eight (26%) of these were classified as spontaneous abortions (loss at <20 weeks) and one (3.2%) as fetal death (loss at ≥20 weeks gestation). In utero exposure ranged from 1 to 3 weeks for all pregnancy losses. The mean gestational age at the time of spontaneous abortion was 7.6 weeks (median 8.0, range 2.5 to 12.5 weeks; n = 7 and one unknown) and at the time of the fetal death was 22 weeks.

The fetal death (case 9) occurred in a 31-year-old woman who had received 44 μg TIW of IFNβ-1a for 5 years. IFNβ-1a was stopped approximately 1 week after conception. At 22 weeks, she miscarried due to an infection following amniocentesis. Examination of the infant revealed no abnormalities.

Previous exposure group. Twenty-two pregnancies occurred in women who had discontinued IFNβ-1a more than 2 weeks prior to conception (44 μg TIW in 10 patients, 22 μg TIW in 11 patients, and 44 μg QW in one patient). Live births occurred in all cases: 20 full-term healthy infants, one premature birth, and one birth-related congenital anomaly (Erb palsy). The premature infant was born to a 38-year-old woman who had received IFNβ-1a, 44 μg TIW, for 24.7 months, discontinued therapy, and conceived approximately 4 weeks later. At 32 weeks' gestation the patient developed hemolysis, elevated liver enzymes and low platelet count (HELLP) syndrome

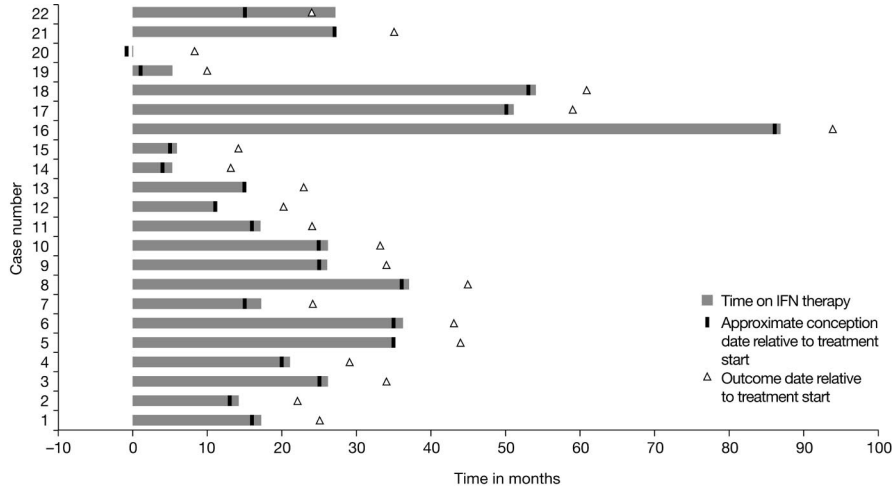

Figure. Course of the 22 pregnancies exposed to interferon (IFN) beta-1a that resulted in healthy full-term infants (cases 1 to 20), a premature healthy infant (case 21), and one congenital anomaly (case 22).

Table 3 *Cases of pregnancy loss in the in utero exposure group**

Case	Maternal age at conception, y	Dose regimen, μg	In utero exposure, wk	Gestational age at pregnancy loss, wk
1	30	22 QW	2	12.5
2	31	22TIW	3	6
3	29	30 QW	1	2.5
4	30	33TIW	Unknown	Unknown
5	26	44 QW	0†	4
6	32	44TIW	3	8
7	19	44TIW	1	8
8	28	44TIW	1	12
9	31	44TIW	1	22

* Loss due to spontaneous abortion (cases 1-8) or fetal death (case 9).
† Drug stopped approximately 4 days before estimated conception date.

and underwent a Cesarean section. The baby initially required intubation and assisted respiration but there were no further complications.

Placebo group. Live births occurred in three of six women receiving placebo, two full-term healthy infants and one infant with a congenital anomaly (cardiac valve defect). The remaining three women elected to terminate their pregnancy, on average 5.5 weeks (median 4.0) after conception.

Discussion. The recommendation against use of IFN during pregnancy stems from animal studies reporting higher than expected abortion rates in primates exposed to human IFNβ during pregnancy. However, the findings are not consistent in all reports and fail to consider the impact of neutralizing antibodies (NAbs) in the dams at the time of abortion. As nonhuman primates develop NAbs to human IFN within 2 to 4 weeks, the attribution of abortions to IFNβ beyond 2 weeks of exposure is open to debate.

Of the 63 pregnancies reported here in the in utero exposure and previous exposure groups, 53 had the potential to go to term and 44 of these (83%) resulted in live infants. There was no apparent difference in pregnancy outcome based on dose of IFNβ-1a administered, although numbers are small.

There was no evidence of teratogenesis during pregnancy. One congenital anomaly was seen in each of the in utero exposure and placebo groups.

The overall rate of pregnancy loss (spontaneous abortions and fetal death) was 16% (9/56) of all pregnancies that could potentially go full term, all occurring in pregnancies exposed to IFNβ-1a. Spontaneous abortion is estimated to occur in 15% to 20% of pregnancies[14-16] and fetal death in 0.65% to 0.7%.[17] The percentage of patients having spontaneous abortions (26%; 8/31) or fetal death (3.2%; 1/31) after in utero exposure to IFNβ-1a therapy in these pooled studies falls within the estimates (2.4% to 27.6% for spontaneous abortion, 0% to 3.47% for fetal death) that could be expected in randomly selected samples of equal size (n = 31) from the general population.

A number of case reports are available in the literature (1992 to 2002) documenting successful pregnancies occurring during, or shortly after, IFNα use in other indications.[18-29] Forty pregnancies were reported, resulting in 41 live births (33 [80%] healthy infants, six [15%] premature births, and two [5%] congenital anomalies). The lack of pregnancy loss may reflect selective reporting of pregnancies with viable outcomes as opposed to all pregnancies.

The apparent lack of major impact of IFN on pregnancy may be due to the large molecular size of IFN preventing transit across the placental barrier.[30,31] In one study of two women, IFNα was below the limits of detection in fetal blood and amniotic fluid.[32] Moreover, the fact that the fetoplacental unit itself is a site of production of IFNα[33,34] and IFNβ[34,35] further suggests that IFN is not harmful to fetal growth.

Other therapies exist to treat MS but mitoxantrone is contraindicated during pregnancy, natalizumab and IFN are both advised against during pregnancy, and glatiramer acetate (GA) has a reported rate of spontaneous abortion of 21% in postmarketing surveillance, similar to findings in this study.[36]

In the current review, the majority of women who decided to continue with their pregnancies had successful outcomes, despite receiving IFNβ-1a at some stage either during or prior to pregnancy. For those who stopped more than 2 weeks prior to conception, even previous prolonged exposure had no apparent impact on pregnancy. The rate of pregnancy loss (spontaneous abortion and fetal death) in those exposed to IFNβ-1a during or just prior to conception was not significantly different from that predicted in the general population, although the power to detect an effect was low. Patients should still be advised to discontinue IFNβ-1a prior to planned pregnancy or if they become pregnant.

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