HIGH LIGHT
CME

The reproductive effects of beta interferon therapy in pregnancy

A longitudinal cohort

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Abstract—*Objective:* To determine whether interferon therapy during human pregnancy increases reproductive risks in women. *Methods:* This longitudinal, controlled cohort study consisted of three groups of women: an exposed group, a disease matched unexposed group, and a healthy comparative group. Subjects were selected from women contacting the Motherisk Program regarding maternal beta interferon exposure, mostly for multiple sclerosis during pregnancy, from 1997 to 2004. After delivery all of the women were re-contacted for a follow-up interview regarding maternal health, pregnancy outcome, and neonatal health. *Results:* The study group (n = 16 women, 23 pregnancies) were exposed to interferon beta-1a (Avonex, Rebif) and interferon-1b (Betaseron). There was a decrease in mean birth weight in the exposed group (3,189 ± 416 g) as compared to healthy controls (3,783 ± 412 g, $p = 0.002$). Women exposed to beta interferon had a higher rate of miscarriages and stillbirths (39.1%) vs healthy controls (5%) ($p = 0.03$), even after correction for potential confounders. There were two major malformations (abnormality in the X chromosome, Down's syndrome) among exposed fetuses. *Conclusions:* Beta interferon therapy in the first trimester of pregnancy appears to be associated with an increased risk for fetal loss and low birth weight.

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First suggested by Jacobs et al. in 1987, interferon beta is currently the most widely used therapy for multiple sclerosis (MS).[1-3] Beta interferon has been shown to reduce the relapse rate, disease activity, and disease progression of active-relapsing MS[1,2,4,5] by decreasing human leukocyte antigen (HLA) expression. While pregnant women with MS do not appear to be more likely to have pregnancy and delivery complications, they exhibit higher relapse rates postpartum.[6,7]

Experimental studies have shown that high doses of beta interferon therapy in pregnant rhesus monkeys (40 times the human recommended dose based on surface area) do not result in teratogenicity but dose-dependent abortive effect after three to five doses.[8]

Similarly, it has been reported that alpha interferons are unlikely to be teratogenic, but may increase the risk of spontaneous abortions and intrauterine growth retardation (IUGR).[9]

The limited human experience with beta interferon is based on case reports only. During phase III of the clinical trials, seven women with MS became pregnant while on interferon, resulting in five normal pregnancies and two miscarriages. In all of the cases interferon was discontinued when pregnancy was recognized.[1] An additional case report described normal pregnancy outcome in a 25-year-old woman treated with interferon beta for retinal necrosis. However, interferon therapy started at 25 weeks of gestation, beyond the period of organogenesis.[10]

Pregnant women receiving interferon are typically advised to discontinue therapy due to lack of reproductive information.[11] However, it has been suggested that interferon use during early pregnancy should not be an indication for voluntary pregnancy termination.[11] We sought to determine whether interferon therapy during human pregnancy is associated with increased reproductive risks among women with MS. This is the first prospective, disease-matched controlled human cohort study on the reproductive effects of beta interferon therapy, primarily for MS.

Methods. The Motherisk Program is a teratogen information and counseling service at the Hospital for Sick Children in Toronto. The service provides counseling to members of the public and health professionals regarding the reproductive safety of drugs, chemicals, radiation, and infection during pregnancy and

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lactation. After the expected date of confinement standard questioners are used for follow-up of pregnancy outcome. The Hospital's Research Ethics Board approved the study protocol. The participating women gave informed consent for the follow-up interview.

Patients. This longitudinal, controlled, cohort study consisted of three groups of women: a beta interferon exposed group, a disease-matched unexposed group, and a healthy control group. Subjects selected for the study were pregnant women who contacted the Motherisk Program regarding maternal beta interferon or Copaxone exposure during pregnancy, between 1997 and 2004. Women using beta interferon in pregnancy formed the study group, while those that discontinued beta interferon or Copaxone prior to conception formed the disease-matched group. A healthy control group was formed from callers to the Motherisk Nausea and Vomiting (NVP) helpline, which counsels pregnant women on the treatment of NVP symptoms.

During the initial contact, pregnancy information was collected. This included general information regarding maternal health and any possible xenobiotic exposure, including drug therapy. After the expected date of confinement the women participating in this study were re-contacted for a follow-up interview. The interviews gathered information regarding maternal health, pregnancy outcome, and neonatal health. All xenobiotic exposures throughout gestation were recorded.

The follow-up interviews documented maternal health problems and their severity, all medications used during pregnancy, prescription and over the counter drugs, alcohol, tobacco, and recreational drug use during gestation. For all exposures, the indication, dose, frequency, and side effects were recorded. We also recorded pre-pregnancy weight, weight at delivery, method of delivery, vaginal or caesarean section, and total length of labor. Women were asked to provide information regarding pregnancy outcome in terms of live birth, miscarriage, stillbirth, gestational age at birth, birth weight, neonatal health, birth defects, and developmental milestones.

The information obtained from the mother was verified, through a written document, by the child's pediatrician or family physician, upon the mother's verbal consent. The physicians were requested to complete a questionnaire stating the baby's birth weight and head circumference, as well as any malformations or medical complications.

Statistical analysis. As a first step, univariate analyses were performed. These procedures included frequency counts, cross-tabulations, and analyses of variance.

Subsequently, multivariate analyses, such as linear and logistic regressions with standard and mixed models, were employed. Because we were interested in accounting for the clustering of births within women and modeling differences among all three groups we used a mixed model with a random intercept for mothers in PROC GLIMMIX and PROC NLMIXED on SAS. GLIMMIX uses a linearization of the model (PQL) to obtain estimates and is more stable and quicker but less accurate. NLMIXED approximates the integral in the likelihood numerically using quadrature to obtain a more accurate solution, but optimization is more difficult.[12,13]

Results. A total of 46 women were recruited and 64 gestations were followed up. The exposed study group (Group 1) consisted of 16 women with 23 gestations. One woman gave information regarding three gestations, 5 women gave information regarding two gestations, and 10 women gave information regarding one gestation (see table 1). Fourteen women received beta interferon for MS, one for the treatment of thrombocytosis, and one for the treatment of essential thrombocythemia. Beta interferon-1a (Avonex) was administered IM, 30 mcg once a week and Rebif ranging from 22 to 44 mcg three times a week, subcutaneously. Beta interferon-1b (Betaseron) was administered subcutaneously ranging from 2 MIU to 6 MIU every other day. The mean gestational duration of beta interferon therapy was 9 weeks, ranging from 2 to 38 weeks. In 21 gestations (all with MS) interferon therapy was terminated during the first trimester of pregnancy. The woman with essential thrombocythemia discontinued therapy at 21 weeks of gestation, while the woman with thrombocytosis discontinued therapy at 38 weeks of gestation.

The disease control group (Group 2) consisted of 12 women with MS with 21 gestations. Six of these women gave information regarding three gestations, three women gave information regarding two gestations, and three women with one gestation. Ten patients had discontinued either interferon therapy or Copaxone for the treatment of MS at least 1 month prior to conception, while one woman discontinued interferon for the treatment of hepatitis C and one woman discontinued drug taken for treatment of a wart on her foot.

The healthy control group (Group 3) consisted of 18 women with 20 gestations. Two women gave information regarding two gestations while 16 women gave information regarding one gestation (see table 1). None of these women had any diseases or major health concerns.

The mean age of exposed women (35.6 ± 5.3 years) was higher than both the disease-matched (30.2 ± 4.8 years) and healthy controls group (33.5 ± 5.6 years) ($p < 0.002$, table 2). The mean pre-pregnancy weight in the exposed group was similar among the three groups (see table 2). Women exposed to interferon beta had nine spontaneous abortions and one fetal death yielding a significantly higher rate of pregnancy loss and lower rate of live birth than the healthy control group (see table 1).

Subsequently, initial analyses for the prediction of non-live births involved the use of a logistic mixed-effects model. However, both PQL and ML estimation with numerical integration failed document variance component due to mothers' clustering once maternal age, gravidity, prior history of lost pregnancies, and study group variables were controlled for. More specifically, the estimate for this variance component obtained by both methods was zero. Given the lack of evidence of dependence due to clustering of multiple births in mothers, a standard logistic regression model was used to evaluate the effects of interest.

Maternal age was positively associated with non-live births: with each year of age a non-live birth is 1.22 times more likely than the year before. No significant effects of gravidity or prior history of lost pregnancies were observed. Of greater interest, mothers in the interferon beta study group were 6.9 times more likely to produce a non-live birth, after controlling for age, gravidity, and prior pregnancy history, an effect that was significant (see table 3). While a higher rate of non-live births was also observed in the discontinued interferon group, this effect did not reach significance (see table 3).

In predicting child birth weight the random intercept, reflecting dependence due to clustering, had a variance of 71,729, which is marginal by the Wald test ($z = 1.52$, $p = 0.06$). However, the Wald test is conservative and power is low at this sample size. The intraclass correlation, controlling for gestational age, maternal weight gain, and exposure group, is 0.53, indicating a relatively strong clustering effect—the birth weights of children born to the same mother are correlated at 0.53 even after controlling for other variables in the model. Hence, it is probably important to retain the random intercept in the model, despite its marginal significance, for the fixed effects estimates to have accurate standard errors and CIs. This anal-

Table 1 *Characteristics of women among the study and control groups*

	Women with disease (mostly MS)		Healthy women
	IFN	No IFN	NVP
Distribution of characteristics	Group 1	Group 2	Group 3
Total number of women*	16	12	18
No. of gestations in the study			
Reporting 1 gestation	10	3	16
Reporting 2 gestations	5	3	2
Reporting 3 gestations	1	6	0
Total no. of gestations	23	21	20
End result of reported pregnancy, n (%)†			
Live birth	12 (54.5)	17 (81.0)	18 (90.0)
Non-live birth	10 (45.5)	4 (19.0)	2 (10.0)
Description of non-live birth, n (%)			
No. of spontaneous abortions	9 (39.1)	4 (19.0)	1 (5.0)
No. of fetal deaths	1 (4.3)		1 (5.0)
End result of pregnancies, history, n (%)			
All non-live births	7 (30.4)	4 (19.0)	2 (10.0)
Combinations—live and non-live	9 (39.1)	5 (23.8)	3 (45.0)
All live births	7 (30.4)	12 (57.1)	15 (75.0)
No. (%) of major malformations	2 (8.7)	1 (4.8)	1 (5.0)
No. (%) of neonates born prematurely‡	2 (8.7)	3 (4.3)	1 (5.0)
No. (%) of smokers	2 (8.7)	1 (4.8)	0 (0.0)
No. (%) of alcohol users	7 (30.4)	2 (9.5)	1 (5.0)

* Forty-five women participated in the study. One woman appears in two groups, Group 1 (1 gestation) and Group 2 (3 gestations). The last gestation for this woman appears in Group 1.
† One missing value case in Group 1.
‡ ≤37 weeks gestation (postconception).

MS = multiple sclerosis; IFN = interferon; NVP = Nausea and Vomiting helpline.

ysis revealed that interferon has an independent and significant negative effect on birth weight (table 4).

There were two major chromosomal malformations among exposed fetuses. The first was an offspring of a woman with MS, with abnormality in the X chromosome and a spontaneous abortion.

The second major malformation was Down's syndrome detected prenatally and the family decided to abort the pregnancy. The woman giving birth to a child with Down syndrome was 29 years old with no previous history or known risk factors for Down syndrome.

Discussion. Previous animal studies and human case reports have suggested that beta interferon is unlikely to cause major malformations, but may increase the risk of spontaneous abortions and IUGR.[9] Our study was conducted to determine whether beta interferon therapy for MS increases the risk of reproductive risks.

In planning this study it was deemed important to try to control for potential confounding effects of maternal characteristics, and hence we also re-

Table 2 *Comparison of maternal and neonatal characteristics and pregnancy outcome among the three groups*

Characteristics/outcome	Group I: Interferon	Group II: Disease matched	Group III: Healthy controls	Significant pair
Age at time of gestation, y, mean SD	35.6 ± 4.5	30.2 ± 4.8	33.5 ± 5.6	1 & 2
Pre-pregnancy weight, lb, mean SD	137.4 ± 27.9	139.6 ± 16.9	150.2 ± 29.3	
Weight gain in pregnancy, lb, mean SD	225.7 ± 15.0	30.2 ± 16.8	44.9 ± 27.9	
Gestational age at time of call, wk	4.2 ± 4.4	2.2 ± 3.8	9.3 ± 3.0	1 & 2, 2 & 3
Child's birth weight, g	3,189 ± 416	3,498 ± 470	3,783 ± 412	1 & 3
Gestational age, wk	37.8 ± 2.3	37.4 ± 2.3	38.2 ± 1.0	

The last three variables refer to live birth only.

Table 3 *Logistic regression for prediction of non-live births*

Predictors	Coefficient B	SE	Wald χ^2	*p*	OR Exp (B)	OR 95% CI Lower	OR 95% CI Upper
Maternal age	0.20	0.09	4.90	0.027	1.22	1.02	1.45
Gravidity	−0.53	0.38	1.89	0.169	0.59	0.28	1.25
No. of prior lost pregnancies	0.56	0.57	0.97	0.326	1.75	0.57	5.33
IFN vs healthy group	1.94	0.90	4.59	0.032	6.94	1.18	40.79
Disease vs healthy group	1.36	1.07	1.63	0.202	3.91	0.48	31.67
Constant	−8.29	3.19	6.76	0.009	—	—	—

IFN = interferon.

cruited a disease-matched group of women with MS who discontinued their interferon therapy prior to conception.

The prospective longitudinal design of this study aimed to ensure that selection and recall bias are not confounding the interpretation. In particular, it has been shown that retrospective studies exhibit higher rates of adverse effects, because women with adverse fetal outcome may be more motivated to report their experience than those who experience normal pregnancy outcome.[14] Yet, not being a randomized trial, the group of women with MS using interferon could be different from the disease-control group in important confounders that may affect the outcome of interest. For this reason we also conducted multivariate analyses to try to address the effects of confounders. Although the mean birth weight of 3,189 g is only 200 g below typical baby birth weight of healthy women, it is worth noting that this is similar to the effect size of heavy maternal smoking on birth weight. Because women in the three groups had clustering of different numbers of offspring, our statistical analyses aimed at addressing this potential bias (i.e., that not every child is an independent observation).

Our analysis suggests that interferon therapy for MS during pregnancy may decrease birth weight even after controlling for important confounders. Our study agrees with previous findings[9] with interferon alpha. Consistent with studies in primates, our study suggests higher rates of pregnancy loss, mainly due to spontaneous abortions, among women treated with beta interferon.

Here again, the association persisted after logistic regression for correction of potential confounders, and after addressing potential effect of clustering.

Although ethanol consumption was significantly more common among women who used beta interferon therapy during pregnancy, the exposure was very mild in all cases (several drinks in pregnancy) and this type of exposure has not been associated with an increased risk of spontaneous abortions.[15] Kesmodel et al. have reported that women consuming ≥5 drinks/week are at increased risk of first trimester abortion.[16] Another study has suggested that moderate alcohol consumption (>3 to 7 drinks/

Table 4 *Linear mixed model for prediction of child birth weight (g)*

Fixed effect	Unstandardized coefficient B	Unstandardized coefficient SE*	*t*	*df*†	*p*	95% CI Lower	95% CI Upper
Gestational age at birth, wk	1,230.38	310.39	30.93	310.9	0.004	59.44	187.32
Mother's weight gain, lb	30.96	20.97	10.33	330.5	0.192	−2.09	10.00
IFN vs healthy group*	−4,440.49	1,490.56	−20.97	340.6	0.005	−748.23	−140.75
Disease vs healthy group†	−830.51	1,600.04	−0.52	280.3	0.606	−411.17	244.15
IFN vs disease group‡	−3,600.98	1,610.65	−20.23	390.7	0.031	−687.76	−34.19
Constant	−1,1170.33	12,090.11	−0.92	310.6	0.362	−3,581.43	1,346.77

Random effect	Variance	SE	Wald z	*p*
Mothers	71,729	47,343	10.52	0.065
Children	62,808	32,746	10.92	0.028

* Computed using the Kackar–Harville method.
† Computed using the Kenward–Rogers method.
‡ Computed from coefficients from preceding two lines of the table.

IFN = interferon.

week) may be associated with increased risk of spontaneous abortion.[17] None of the women in our study reported consumption of alcohol in similar amounts.

As women in the healthy control group called later in pregnancy, there is a possibility that some miscarriages were missed. Our study is limited by its small sample size and by potential confounders not controlled for in our analysis. However, pregnancy exposure to beta interferon is a relatively uncommon event. Often women are advised to discontinue interferon prior to conception, making it challenging to recruit women who have taken the drug in pregnancy. Furthermore, we did not have measured disease activity and, although we tried to address a variety of confounders, it is possible that women receiving beta interferon differed from those not receiving the drug in confounders not controlled by us. It does not appear likely, though, that a randomized trial of interferon vs no therapy will be conducted in pregnancy.

The results of our study suggest that women who become pregnant while taking beta interferon should not terminate pregnancy but rather discontinue the drug until delivery. Discontinuing beta interferon therapy during gestation should not necessarily increase the risk of relapse of MS, as pregnancy tends to reduce such risk.[7,18]

It appears that labor is followed by an increase in the relapse rate 6 months postdelivery. Women should be therefore advised to resume interferon therapy very soon after delivery if they do not intend to breastfeed.

Future studies should aim at recruiting larger cohorts of women for both the study and disease-matched groups.

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