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Risk of Birth Defects Associated with Nelfinavir Exposure During Pregnancy

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Objective:

To examine the human teratogenic risk of the HIV protease inhibitor VIRACEPT®(nelfinavir mesylate), which was introduced in the US in 1997.

Methods:

This study uses a subset of the data from the Antiretroviral Pregnancy Registry (APR), which is designed to monitor prenatal exposures to antiretroviral therapy and detect a potential increase in the risk of birth defects. The APR uses a prospective exposure-registration cohort design in which health care providers register pregnant women with prenatal exposures to any antiretroviral therapy, report data on exposure throughout pregnancy, and provide birth outcome data.

For this study, all pregnancies exposed to nelfinavir, used alone or in combination, were extracted from APR and analyzed. The prevalence of birth defects is compared to the CDC's population-based surveillance system. Statistical inference is based on exact methods for binomial proportions. For all defects combined, a cohort of 200 is required to detect a doubling of risk compared to CDC's expected prevalence, with 80% power and a Type I error rate of 5%. For specific defects, the power varies with the frequency of the defect in the population and the size of the exposed group.

Results:

Through January 2002, the APR has monitored 915 live births exposed to nelfinavir. Among 301 first trimester exposures, there were 9 birth defects, for a prevalence of 3.0% (95% CI = 1.4, 5.6). This rate is not significantly different from the CDC's system with a prevalence of 3.1 per 100 live births (95% CI = 3.1, 3.2). There is no consistent pattern among reported birth defects. Additionally, the prevalence of birth defects among offspring of women with first trimester exposure to nelfinavir is not significantly different from the prevalence of second/third trimester exposures to nelfinavir (risk ratio = 1.7, 95% CI = 0.7, 3.9).

The prevalence of prematurity was 11.8% which is similar to the US national average of 11.6% (NCHS, 2002). The prevalence of low birth weight was 15.0% which is higher than the US national average of 7.6% (NCHS, 2002).

Table 1. Enrollment Characteristics of Cases with any Nelfinavir Exposure During Pregnancy

Characteristic	Pregnancies Enrolled N=944 (91.7%)		Lost to Follow-up N=85 (8.3%)	
Age				
Mean (standard error)	28.1	(0.2)	27.5	(0.6)
Median (interquartile range	28.0	(9.0)	27.0	(8.0)
Minimum - Maximum	15 - 43		16 - 39	
Missing	4		2	
Race				
White	187	(19.8%)	18	(21.2%)
Black	504	(53.4%)	39	(45.9%)
Hispanic	197	(20.9%)	15	(17.6%)
Other	38	(4.0%)	3	(3.6%)
Unknown	18	(1.9%)	10	(11.8%)
CD4+ cell count at start of pregnancy				
<200/mm^3	211	(22.4%)	14	(16.5%)
200-499/mm^3	462	(48.9%)	37	(43.5%)
>500/mm^3	249	(26.4%)	24	(28.2%)
Missing	22	(2.3%)	10	(11.8%)
Clinical categories at start of pregnancy				
Asymptomatic, acute (primary) HIV	679	(71.9%)	50	(58.8%)
Symptomatic	109	(11.5%)	10	(11.8%)
AIDS-indicator conditions	124	(13.1%)	11	(12.9%)
HIV postexposure prophylaxis	3	(0.3%)	1	(1.2%)
Unknown	29	(3.0%)	13	(15.3%)

Figure 1. Year of Enrollment in the Antiretroviral Pregnancy Registry. Cases with any Nelfinavir Exposure During Pregnancy.

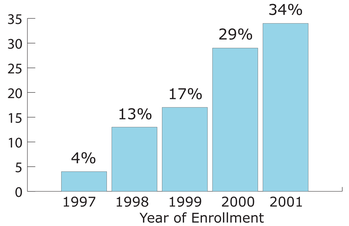

Table 2. Summary of Pregnancy Outcomes By Antiretroviral Treatment Regimen - Cases with any Nelfinavir Exposure During Pregnancy

	Outcomes with Birth Defects Spontaneous/ Induced Abortions			Outcomes w/o Birth Defects Specified				
	Live Births	Still-birth		Live Births	Spontaneous Losses	Still-birth	Induced Abortions	Overall
Number of Outcomes	20	1	0	895	11	14	19	960
Earliest Exposure[2]								
First Trimester:	8	1	0	293	7	6	18	333
Second/Third Trimester:	11	0	0	598	4	8	1	622
First Trimester								
PI(s) only	0	0	0	2	0	0	0	2
PI(s) + NRTI(s) combination	6	1	0	251	5	5	14	282
PI(s) + nnRTI(s) combination	0	0	0	1	0	1	0	2
PI(s) + NRTI(s) + nnRTI(s) combination	2	0	0	38	2	0	3	45
PI(s) + NRTI(s) + NtRTI(s) combination	0	0	0	1	0	0	1	2

Note: 5 cases with unspecified trimester of exposure

PI	(protease inhibitor)	includes: amprenavir, indinavir, nelfinavir, ritonavir, saquinavir, and lopinavir/ritonavir
NRTI	(nucleoside analog reverse transcriptase inhibitor)	includes: abacavir, didanosine, lamivudine, stavudine, zalcitabine, and zidovudine
nnRTI	(non-nucleoside analog reverse transcriptase inhibitor)	includes: delavirdine mesylate, efavirenz, and nevirapine
NtRTI	(nucleotide analog reverse transcriptase inhibitor)	includes: tenofovir DF

Table 4. Gestational Age at Delivery and Birth Weight by Earliest Trimester of Exposure for Cases with any Nelfinavir Exposure During Pregnancy*

	Gestational Age <32	Gestational Age <37	Birth Weight <1500	Birth Weight <2500
Overall	12/861 (1.4%)	102/861 (11.8%)	14/838 (1.7%)	126/838 (15.0%)
First Trimester	4/285 (1.4%)	37/285 (13.0%)	4/276 (1.4%)	39/276 (14.1%)
Second Trimester	8/393 (2.0%)	54/393 (13.7%)	10/385 (2.6%)	66/385 (17.1%)
Third Trimester	0	11/179 (6.1%)	0	21/173 (12.1%)

* Data in table restricted to singleton live births without reported birth defects.
Excluded: 4 cases with unspecified trimester of exposure
1 case with missing gestational age
24 cases with missing birth weight

Table 3. Confidence Intervals for Birth Defects - Cases with any Nelfinavir Exposure

	Overall
Number of Live Births	915
Number of Live Births with at least one defect	21 (2.3%)
95% Confidence Intervals for % of Birth Defects for exposures in:	
First Trimester	9/301 (3.0%) 1.4 - 5.6
Second/Third Trimester	11/609 (1.8%) 1.6- 3.1
Any Trimester *	21/915 (2.3%) 1.4 - 3.5
Risk of defects for first trimester exposures relative to second/third trimester exposures	1.7 (0.7, 3.9)

* 1 case had unspecified trimester of exposure.

Conclusions:

Because antiretroviral therapy is recommended for all HIV-infected pregnant women, and because nelfinavir is the most commonly reported protease inhibitor in pregnancy, information on the effects on fetal outcome is critical.

The results of this study suggest that the overall risk of birth defects among infants exposed prenatally to nelfinavir are not significantly higher than the CDC's population-based birth defects surveillance system. The number of cases in our study is only sufficient to detect a two-fold increase in the overall risk of birth defects, and the numbers are not sufficient to detect the risk of individual defects.

While nelfinavir should only be used in pregnant women if the benefits outweigh the potential risk to the fetus, the findings from this study should provide some assurance to health care providers and their HIV-infected pregnant patients.

The Antiretroviral Pregnancy Registry is ongoing; exposures to all antiretroviral therapies during pregnancy may be reported by calling 800-258-4263 in the US and Canada and 910-256-0238 internationally or by emailing registry@pharmaresearch.com.