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In Utero Exposure to Zidovudine and Neonatal Heart Anomalies in the ANRS-EPF/PRIMEVA

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OBJECTIVE

To explore associations between in utero exposure to zidovudine and postnatal heart anomalies in the national French Perinatal cohort (ANRS EPF CO1/CO11) and the nested PRIMEVA ANRS 135 randomized trial.

Congenital Heart Defects in the French Perinatal Cohort EPF

METHODS

• ***The French Perinatal Cohort (EPF)***

- HIV-infected women and their children included since 1986 in 90 French maternity centres

- children followed until 2 years (uninfected) and 18 years (infected).

▪ ***Study population:*** All live births exposed to antiretrovirals during pregnancy, between 1994 and 2010. **→N= 12,888**

▪ ***Main outcome***: Congenital heart defects, diagnosed during the 2 years of follow-up (EUROCAT and anatomic and clinical classification)

▪ ***Statistical analysis***: Logistic regression models.

Table 2 – Description of Congenital Heart Defects

	N
Ventricular Septal Defects	
Perimembranous	17
Muscular	31
Not specified	42
Atrial Septal Defect	9
Major Congenital Heart Defects*	
Functionally univentricular hearts	
Hypoplastic left heart syndrome	1
Pumonary valve atresia with intact ventricular septum	1
Anomalies of atrio-ventricular junction	
Complete atrio-ventricular septal defect (in a child with associated defects)	1
Anomalies of ventriculo-arterial connections	
Tetralogy of Fallot	1
Anomalies of the extrapericardial arterial trunks	
Coarctation of the aorta	7
Patent ductus arteriosus (in term infants, necessitating surgery, one of them had associated defects)	2
Right pulmonary artery absent	1
Pulmonary valvar anomalies	
Pulmonary valvar stenosis : congenital	5
Dysplastic pulmonary valve	1
Aortic valvar anomalies	
Bicuspid aortic valve	1

* defined as heart defects after exclusion of ventricular septal defects and atrial septal defects.

Table 1 – Association between exposure to zidovudine in the first trimester and congenital heart defects, 1994-2010, EPF CO1/CO11

Type of CHD	Exposure 1st trimester	% CHD	Multivariable analysis AOR[1]	95% CI	p
All CHD					<0.001
	No zidovudine	0.74	1		
	Zidovudine	1.50	**2.2**	**[1.5-3.2]**	
Ventricular septal defects					<0.001
	No zidovudine	0.55	1		
	Zidovudine	1.13	**2.3**	**[1.4-3.5]**	
Major CHD[2]					0.04
	No zidovudine	0.11	1		
	Zidovudine	0.31	**2.6**	**[1.1-6.6]**	

1 AOR: adjusted Odds Ratio, adjusted on age, geographical origin, year of birth, parity, intravenous drug use, CD4 cell count, gender of neonate; 2 Major congenital heart defect, defined as CHD after exclusion of ventricular septal defects and atrial septal defects; CI: confidence interval. N unexposed to zidovudine = 9,626; N exposed to zidovudine in the first trimester = 3,262.

RESULTS

• **Overall congenital heart defect rate** among livebirths without chromosomal anomalies= **0.93% [95%CI 0.76-1.10]**

→ Higher than in a French population based study: 0.68% [0.67-0.73]

→ Tends to be higher among females (1.1%) than among males (0.8%) (p=0.06)

•**Congenital heart defects significantly associated with 1st trimester exposure to zidovudine (table 1)**

→ concerned ventricular septal defects, but also major defects defined by exclusion of ventricular septal defects and atrial septal defects.

→ independent from other drugs taken simultaneously and no interactions between zidovudine and gender, year of birth or other drugs.

•**Detail of the 120 congenital heart defects:**

→111 diagnosed in the first 6 months, and 68 with full diagnosis at birth.

→ 4 children died, and 11 underwent surgery at birth.

Postnatal Heart Anomalies In the nested PRIMEVA randomized trial

METHODS

• ***The PRIMEVA trial (fig 1)***

-Randomized : monotherapy (lopinavir/ritonavir) and triple therapy (LPV/r + zidovudine/lamivudine) started at 26 WG.

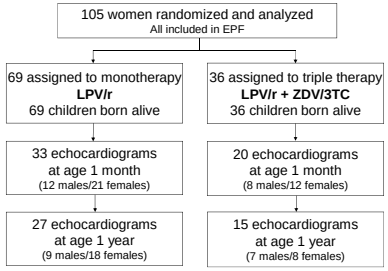
- Primary outcome : viral efficacy

- Secondary outcome: Echocardiograms planned for all infants at 1 month and 1 year of age.

▪ ***Study population***: All infants with at least one echocardiogram.

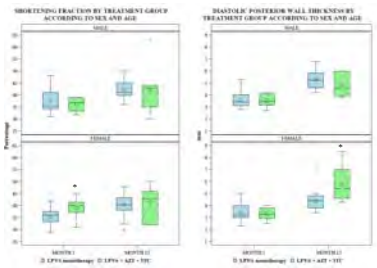
▪ ***Statistical analysis***: Wilcoxon non-parametric test.

Fig1 – Flow chart of Primeva ANRS 135 trial



Children who did not undergo echocardiograms either (1) had the exam outside of the time limit defined by protocol, (2) declined the exam, or (3) were lost to follow-up. Characteristics of mothers and children did not differ between those who underwent echocardiogram and those who did not.

Fig2 – Comparison of two echocardiogram fonctional parameters between children exposed and non exposed to nucleosides (Primeva ANRS 135)



* p = 0.01 * p = 0.01

RESULTS

•Triple therapy (including AZT+3TC) versus monotherapy (no nucleosides) was associated in females with:

→ **higher shortening fraction at one month** (median: 39.9% vs 36.0%, p = 0.01)

→ **thicker posterior wall at one year** (median: 5.4mm vs 4.4 mm, p = 0.01)

•These associations were independent from level of hemoglobin at birth.

• There was no significant difference in functional parameters between groups among males.

ABSTRACT

Background – Antiretroviral regimens during pregnancy have proved their efficacy in the prevention of mother-to-child transmission of HIV. Several studies recently pointed out association of in utero zidovudine with an increased risk of congenital heart defects and with modification in infant myocardial mass and contractility. We aimed to explore in detail this association, among the EPF national cohort and the Primeva nested randomized trial.

Methods – Since 1986, EPF-CO1/CO11 prospectively enrolled near 20000 mother-child pairs from all pregnant HIV-infected women delivering in 90 centers throughout France. The associations between ARV and each kind of congenital defects have been previously reported in EPF among the 13 124 livebirths between 1994 and 2010. For the present study, all CHD were reviewed, monitored on sites to obtain additional information, and adjudicated by a CHD specialist, blinded to in utero exposures. Echocardiogram was planned in infants at 1 and 12 months in a trial linked to EPF, the phase II/III ANRS-135 PRIMEVA trial. Women were randomized to receive in the last trimester of pregnancy either LPN/r alone (group 1; n=69) or AZT+LMV+LPN/r (group 2; n=36).

Results – Zidovudine (versus no zidovudine) in the first trimester was significantly associated with congenital heart defects before and after adjustement for potential confounding variables and concomittant ARV medications: 1.5% vs 0.7%, p <0.001; AOR = 2.2 [1.5-3.2]. This association concerned ventricular septal defects: 1.1% vs 0.6%, p = 0.001, and major CHD (not including VSD and ASD) : 0.31% vs 0.11%, p = 0.02, although this concerned small numbers. In the Primeva trial, LV fractional shortening was higher in girls exposed to nucleosides in group 2 than to LPV monotherapy in group 1 (40% vs 36%; p = 0.01 at 1 month), and the posterior wall thicker at 1 year (5.4mm vs 4.4mm, p = 0.01). No differences were observed among boys between the two groups.

Conclusion – This study shows a specific association between in utero exposure to zidovudine and CHD, as has been evoked in previous smaller studies, and is the first randomized controlled trial to find an association between combination therapy and modification of heart function. This should be taken into consideration, given the large number of children exposed to perinatal zidovudine in the world. Potential mechanisms underlying these associations must be investigated.

CONCLUSION

• **Exposure to Zidovudine**

→In the first trimester of pregnancy was significantly associated with heart defects in the EPF cohort.

→In the third trimester of pregnancy was associated with modification in heart function parameters among females but not among males.

This difference between genders has already been described in an animal study (Chan et al, 2007) and in an observational study (Lipschultz et al, 2011).

•Potential mechanisms underlying these associations, involving myocardial growth and remodeling, must be investigated.

•This alert reinforces recent WHO recommendations for PMTCT, which no longer consider zidovudine to be the first-line ARV during pregnancy.