

ORIGINAL ARTICLE

Sudden infant death syndrome in infants born to HIV-infected and opiate-using mothers

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7 June 2007**Objective:** This study was undertaken to determine the role of opiate use during pregnancy as a predisposing factor for sudden infant death syndrome (SIDS) in infants born to HIV-infected mothers.**Methods:** In order to identify all infant deaths and their cause and association with maternal opiate use, the data of a nationwide prospective cohort study of HIV-infected mothers and their children were extracted and analysed for a 13-year period.**Results:** 24 (5.1%) infant deaths were observed out of 466 infants followed up until death or at least 12 months of life. 3 (0.6%) of them were due to non-accidental trauma and were not associated with maternal opiate use. 7 (1.5%) died due to SIDS, which was confirmed by autopsy. All SIDS cases occurred in infants born to mothers reporting use of opiates during pregnancy (n = 124). The relative risk of SIDS compared to the general population was 18 (95% CI 9 to 38) for all infants of HIV-infected mothers, and 69 (95% CI 33 to 141) for those with intrauterine opiate exposure (p < 0.001).**Conclusions:** Compared to the Swiss general population, the risk for SIDS in this cohort of infants born to HIV-infected mothers was greatly increased, but only for mothers reporting opiate use during pregnancy. This effect appeared not to be mediated by prematurity, low birth weight, perinatal HIV infection or antiretroviral drug exposure.

The evidence for a link between opiate use and sudden infant death syndrome (SIDS) in the general infant population is inconsistent.^{1–4} In infants of HIV-infected mothers, an increased rate of verified SIDS possibly related to maternal opiate use was noted in several cohorts, namely 5/1000 live births in the European Collaborative Study,⁵ 6/1000 in France⁶ and 14/1000 in Switzerland.⁷ Thus, a detailed analysis of this link in the Swiss cohort was thought to be worthwhile.

This study was undertaken to determine the frequency and causes of non-HIV-related infant deaths in the Swiss Mother & Child HIV Cohort (MoCHiV), with special attention given to SIDS and the role of maternal heroin and/or methadone consumption during pregnancy. In addition, the role of non-accidental trauma and of potential risk factors such as prematurity, low birth weight, maternal HIV infection and antiretroviral medication, were explored.

METHODS

MoCHiV is a nationwide multicentre cohort study on vertical HIV transmission in Switzerland. Since 1986 newborn infants of HIV-infected mothers have been enrolled at birth and followed up prospectively. In 1989 enrolment of women during pregnancy and follow-up of mother-child pairs were begun. The setting and methods of the study have been published previously.^{7, 8} Baseline data were registered at enrolment, that is, during pregnancy or at birth, on a case report form which was completed by the obstetrician and the paediatrician. Extensive data were collected on medical and social history, physical examination, and laboratory tests of the mother and neonate.

Maternal opiate use, as intravenous injection of heroin or oral consumption of methadone in a controlled substitution programme, was identified by self-report or indication by the addiction clinic. Many of these heavily addicted women used intravenous heroin in addition to methadone substitution or consumed illegal street methadone. For this reason, separation

into heroin-using and methadone-using mothers was not possible. Withdrawal symptoms in the newborns were systematically looked for. All women were classified as: opiate use during pregnancy, opiate use before pregnancy only, no opiate use ever or unknown. No regular screening of maternal urine or meconium was performed. Further information on clinical course and laboratory tests in infants was collected from the responsible paediatrician by means of a follow-up form at 6 weeks, 6 months, 1 year and 2 years after birth.

Cause of death was ascertained by review of the medical history and autopsy reports. Investigation of the death scene was conducted as performed in all unexplained deaths in Switzerland. Thus, classification as SIDS implied the sudden, unexpected death of a previously healthy infant without clinical or laboratory evidence of HIV infection, an autopsy revealing no explanation for the death and an unremarkable investigation of the death scene. All mothers gave verbal informed consent. The study was conducted according to the guidelines of the Declaration of Helsinki of 1975 as amended in Venice, Hong Kong and Somerset West.

Data for a 13-year period (1 January 1986 to 31 December 1998) were extracted from the database and analysed to identify all cases of death during the first year of life, verifying causes of death and exploring the role of potential risk factors for SIDS.

Several mothers in the cohort were observed for more than one pregnancy or had multiple births. To avoid bias, only the firstborn registered child of each mother was considered in the analysis.

The overall risk of SIDS in the study cohort and in the opiate use subgroup was compared to the overall SIDS incidence in the Swiss general population of 0.82/1000 (875 cases of SIDS in 1 061 884 live births) for the period 1986 to 1998 (personal

Abbreviation: SIDS, sudden infant death syndrome

Table 1 Maternal age, birth weight, gestational age and completeness of follow-up versus opiate use

Maternal opiate use	Number of infants	Maternal age (years), mean (SD)	Neonatal birth weight (g), mean (SD)	Gestational age at birth (weeks), mean (SD)	Number with complete follow-up (%)
During pregnancy	138	27.5 (4.2)	2652 (534)*	37.7 (2.4)**	124 (89.9)***
Before pregnancy only	139	27.5 (3.9)	2974 (599)	38.2 (2.6)	125 (89.9)***
Never	231	28.2 (4.6)	3129 (577)	38.3 (2.4)	179 (77.5)***
Unknown	55	29.0 (5.2)	3059 (837)	38.1 (2.2)	38 (69.1)***

* $p < 0.001$ (ANOVA vs the other three groups); ** $p = 0.02$ (ANOVA vs the other three groups); *** $p = 0.001$ (χ^2 for heterogeneity).

communication: E Wüest, Swiss Cause of Death Statistics, Swiss Federal Statistical Office, 2010 Neuchatel, Switzerland).

Approximate 95% confidence intervals (CI) were calculated for proportions and relative risk (risk ratios) using the program EPI INFO 2000 distributed by the Centers for Disease Control and Prevention in Atlanta, USA. Associations were tested using Fisher's exact test, analysis of variance (ANOVA) or Wilcoxon test where appropriate.

RESULTS

Overall, the database contained information on 627 children of 563 HIV-infected mothers. Of these, 12 mothers had twin pregnancies and 108 more than one pregnancy (one mother with four, six mothers with three, and 43 mothers with two pregnancies). Applying the single mother-child pair criterion, 58 younger siblings and six second born twins were eliminated from the analysis, leaving 563 evaluable pairs.

Of the 563 mothers, 138 (24.5%) reported opiate use during pregnancy and 139 (24.7%) only before pregnancy, whereas 231 (41%) never used opiates. Fifty five (9.8%) were classified as unknown because conclusive information was missing. Table 1 shows maternal age, birth weight and gestational age for the different subgroups. Infants of mothers reporting opiate use during pregnancy had significantly lower gestational age and birth weight but no difference in maternal age compared to the other three groups. The children included 280 males and 283 females. A total of 466 children (83%) from the entire cohort enrolled at birth could be followed up until at least 12 months of age or until death. Loss to follow-up was heterogeneous among maternal opiate use categories but smallest for infants of mothers reporting opiate use (table 1).

A total of 24 (5.1%) deaths during the first year of life were recorded in the study cohort. Causes of death grouped by maternal opiate use category are detailed in table 2. Seven infants died of SIDS at a median age of 3 months (range 1–7 months). The SIDS incidence in the total cohort was 14.9/1000 live births (95% CI 7 to 32/1000) and 56.5/1000 live births (95% CI 23 to 113/1000) in the subgroup with ongoing opiate use during pregnancy. Compared to the SIDS incidence in the Swiss general population of 0.82/1000, the relative risk was 18 (95% CI 9 to 38) for infants of HIV-infected mothers and 69 (95% CI 33 to 141) for infants with intrauterine opiate exposure ($p < 0.001$).

Furthermore, potential risk factors for SIDS such as male sex and younger maternal age showed no significant association. Neither did perinatal antiretroviral medication used for treatment of the mother or prevention of vertical transmission (table 3). Among infants of mothers reporting opiate use, prematurity was less frequent in those who died of SIDS (14.3%) than in those surviving (24.1%), although this association was not significant. The same was true for low birth weight (14.3% in SIDS victims vs 31.6% in survivors).

DISCUSSION

The role of opiate use by mothers during pregnancy, as a predisposing factor for SIDS, is still a matter of debate. Whereas early descriptive studies of cohorts without concurrent controls of infants born to mothers with regular opiate use during pregnancy reported SIDS rates of 21/1000¹ and 40/1000,² more recent studies were unable to find an association between maternal opiate use and SIDS after controlling for potential confounders such as maternal smoking, prematurity or low birth weight.^{3–4} These studies, however, were either based on linking birth and death registers⁴ or used a case control design.³ As an inherent feature of studies linking birth and death registers, the rate of loss to follow-up due to migration out of the study area could not be quantified. This could lead to unproportionally increased SIDS in opiate-exposed infants dying outside the study area compared to non-opiate-exposed infants. Hence, this factor would tend to diminish the estimated risk of SIDS associated with opiate use by mothers during pregnancy.

In the present study, a cohort of infants with known exposure status for intrauterine opiates was followed up prospectively. Loss to follow-up was only 10% in infants of opiate-using mothers. Opiate exposure status was identified by self-report and ascertained by experienced treating physicians in the context of a prospective study.

The results reveal an astonishingly increased incidence of SIDS of 14.9/1000 live births in our prospective cohort of infants born to HIV-infected mothers. This rate is identical to the figure found in our earlier report,⁷ when the cohort was about half the present size, but is considerably higher than the SIDS rate observed in the European Collaborative⁵ and in the French prospective⁶ studies. In addition, an increased rate of infant deaths due to non-accidental trauma was detected, accounting for 12.5% of infant deaths, confirming results from the

Table 2 Causes of death in infants who died

Maternal opiate use	Number of infants	Total number of deaths	SIDS	HIV infection	Non-accidental trauma	Other causes*
During pregnancy	124	10	7	2	1	0
Before pregnancy only	125	4	0	4	0	0
Never	179	8	0	6	1	1
Unknown	38	2	0	0	1	1

*Neonatal septicaemia, cardiac anomaly.

Table 3 Possible risk factors for SIDS in infants of HIV-infected mothers

Infants	n	Sex (% male)	Maternal age (years), mean (SD)	Prematurity (<37 weeks, %)	Low birth weight (% <2500 g)	Antiretroviral medication perinatally (%)	Opiate use during pregnancy (%)
Died of SIDS	7	71.4*	27.3 (4.5)*	14.3*	14.3*	0*	100**
Survived ≥1 year	442	50.2	27.7 (4.3)	17.4	18.1	14.7	22.5

*Difference not significant compared to surviving infants; **p=0.001 compared to surviving infants.

American P²C² study,⁹ where 20% of infant mortality in infants of HIV-infected mothers was due to accidental or non-accidental trauma.

Although increased rates of prematurity and low birth weight as well known effects of opiate use during pregnancy were observed in our cohort, the increase in SIDS rate appeared not to be mediated through these recognised risk factors. In fact, among infants of opiate-using mothers, prematurity and low birth weight were more frequent in those who survived to 12 months of age than in those who died of SIDS.

The results do not indicate a role of maternal HIV infection per se as a risk factor for SIDS. This contradicts a suggestion based on observations in Rwanda.¹⁰ SIDS in our cohort occurred exclusively in the subgroup of mothers known to have pursued use of opiates during pregnancy. In this subgroup, SIDS incidence was 56.5/1000 live births.

Yet another factor causing sudden unexpected death in exposed infants could be mitochondrial toxicity due to antiretroviral therapy during pregnancy and neonatal zidovudine prophylaxis.¹¹ However, none of the infants who died of SIDS in the present study had been exposed to any antiretroviral drugs. They all had been born before December 1993, which is well before the results of the ACTG076 trial showed the efficacy of zidovudine prophylaxis. Up until this publication in 1994, antiretroviral treatment during pregnancy was mostly avoided in Switzerland.

Two important risk factors have not been considered in this study. The "Back to Sleep" campaign introduced in 1994 led to a 50% reduction in SIDS deaths.¹² This campaign started during the last third of the study period. Hence, sleeping position has not been assessed in this study. Thus, a possible higher rate of prone sleeping position in infants with intrauterine opiate exposure may have contributed to the elevated risk. However, since the SIDS incidence in the Swiss general population before

the "Back to Sleep" campaign was about 1 to 2/1000, even if all opiate-using mothers ignored the new advice, an increase in risk of the observed magnitude could not be explained.

Maternal smoking, nowadays seen as the primary modifiable risk factor for SIDS,¹³ could not be assessed in this study as a reliable smoking history was lacking for many mothers and was almost uniformly positive when available in opiate-using mothers. Thus, smoking may have contributed to the elevated risk. However, since the relative risk for SIDS attributable to maternal smoking is in the order of 2 to 8¹⁴ depending on intensity of smoking, the possible contribution of smoking appears insufficient to explain the relative risk of 69 found to be associated with opiate use in the present study. Breast feeding as a potential protective factor is unlikely to have played a significant role in this cohort, since breast feeding has always been strongly discouraged in HIV-infected mothers and only a small minority of mothers were known to breast feed their infants.

Our observations lead to the conclusion that maternal use of opiates during pregnancy per se confers a highly elevated risk of SIDS in infants born to HIV-positive mothers. Some hypotheses can be formulated. In animal studies, intrauterine exposure to opiates has been found to impair the development of normal neuronal density and morphology.¹⁵ On the other hand, histopathological studies in victims of SIDS have described hypoplasia¹⁶⁻¹⁷ of the arcuate nucleus and abnormalities of serotonergic neurons in the medulla oblongata.¹⁸ It might therefore be of interest to study the fetal effects of opiates on this specific region as well as on serotonergic neurons. Recently, a relationship between genetic variants of cardiac sodium channels associated with long QT syndrome and sudden infant death has been established.¹⁹ Interestingly, QT interval prolongation is observed in methadone maintenance patients.²⁰ Thus, an effect on the QT interval could be a possible link between opiate exposure and the highly elevated risk of SIDS. Because SIDS is still a major cause of infant mortality in the first year of life, further investigation is mandatory.

What is already known on this topic

- The evidence for a link between opiate use and sudden infant death syndrome (SIDS) in the general infant population is inconsistent.
- An increased rate of non-HIV-related deaths occur in infants born to HIV-infected mothers, some of which are due to SIDS.

What this study adds

- Maternal use of opiates during pregnancy confers a highly elevated risk of SIDS in infants born to HIV-infected mothers.
- This effect appears not to be mediated by prematurity, low birth weight, perinatal HIV infection or antiretroviral drug exposure.

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