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Mother-to-child transmission of human immunodeficiency virus in Italy: temporal trends and determinants of infection

The Italian Collaborative Study* on HIV infection in pregnancy

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In order to analyse temporal trends in vertical transmission rates of human immunodeficiency virus (HIV) and determinant of congenital HIV infection in Italy, we have considered data from a network of hospitals co-operating in the Italian Collaborative Study on HIV infection in pregnancy, conducted between 1988 and 1995. A total of 1040 women entered the study. The HIV-1 status of the babies was known in 848 cases (81.5%). Transmission rates were highest in the period 1988–1991, then tended to decrease and in 1995 the rate was 9.7 per 100 children (this finding, however, was based on only six infected children and the trend was not statistically significant). Considering the overall series, the risk of vertical HIV transmission was higher in women with low CD4 count in pregnancy [odds ratio (OR) <400 versus ⩾400 1.8, 95% confidence interval (CI) 1.1–2.9]. In comparison with vaginal delivery the risk of transmission was 0.3 (95% CI 0.1–0.5) and 0.6 (95% CI 0.3–1.2) respectively for elective and emergency delivery. In comparison with women who delivered at term (⩾37 gestation weeks) the OR of HIV infection of the babies for the whole series was 2.2 (95% CI 1.3–3.6) in women who delivered preterm. Similar findings emerged when the analysis was conducted considering, separately, subjects observed in the period 1988–1991 and 1992–1995. The frequency of Caesarean section increased from 26.5% of deliveries in 1988–1991 to 36.2% in 1992–1995. Consequently, most temporal differences disappeared after standardization for mode of delivery, but the rate in 1995 was still lower than in 1988–1994.

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Introduction

The rate of vertical transmission of human immunodeficiency virus (HIV) in Europe is declining. Studies in the mid-1980s reported a 25–30% incidence of congenital HIV infection, but surveys in the early 1990s have found a 10–15% mother-to-child transmission rate (European Collaborative Study, 1994, 1996; European Collaborative Study and the Swiss HIV Pregnancy Cohort, 1997; Maguire *et al*., 1997; Byers *et al*., 1998). This decline may depend on the changing characteristics of the population of HIV-infected pregnant women, with an increase in women with asymptomatic disease, or on changes in obstetric management with interventions aimed at reducing the vertical transmission of the virus. Some studies have indicated that delivery by Caesarean section reduces the incidence of congenital infection (Dunn *et al*., 1994; European Collaborative Study, 1994) and a randomized trial found that giving zidovudine to the mother reduced the risk of transmission by 70% (Connor *et al*., 1994). The encouraging results of these studies may have led to an increased number of women with HIV being delivered abdominally or receiving prophylactic antiretroviral therapy (Kind *et al*., 1998).

In this paper, we analyse the temporal trends in the rate of vertical HIV transmission in Italy by looking at a data set of over 1000 pregnant HIV-positive women collected retrospectively (1988–1990) and then prospectively (1990–1995) by a multicentre study group (Italian Collaborative Study), which included 13 major obstetric departments. The data on this large number of women provides an opportunity to evaluate the changes in the characteristics of the HIV-infected obstetric population and the impact of obstetric management in different calendar periods.

Materials and methods

Between January 1988 and June 1995 we studied consecutive HIV infected women who delivered singleton live babies in 13 obstetrics departments in Italy (Obstetrics Departments of Bari, Bologna, Brescia, Firenze, Napoli, Padova, Pavia, Turin, Roma – Gemelli, La Sapienza – Milan – Mangiagalli, S. Paolo, Sacco). Data were collected on general risk factors, clinical and obstetric data during antenatal visits and hospital stay for delivery. Information was recorded about delivery, vaginal, elective or emergency (i.e. during labour, regardless of the status of membranes) Caesarean section, and the neonate (birth

weight, sex, gestational age). Data were collected on use of intravenous drugs (heroin) and antiretroviral drugs (zidovudine) in pregnancy.

The diagnosis of maternal HIV infection was based on HIV antibody status by ELISA and Western blot commercial kits. Mothers were characterized by the CD4+ lymphocyte count, done close to delivery (mostly during the third trimester of pregnancy). Lymphocyte counts have been available for all women since 1989.

If a woman delivered more than one baby in different pregnancies during the study period, only information regarding the first singleton livebirth was considered.

A total of 1040 women entered the study (mean age 26 years, range 16–44). At the time of data analysis, the HIV-1 status of the babies was known in 848 cases (81.5%). Infants were not breast fed. They were followed up till 18 months. Children were monitored for signs and symptoms of possible HIV-related illness. Serological tests (ELISA and Western blot commercial kits) were repeated at 12 and 18 months. A child was classified as HIV infected if he/she fulfilled one of the following conditions: (i) positive serological test at 18 months or more; (ii) developed clinical signs and symptoms or died because of clinical conditions related to AIDS before 18 months.

A total of 573 cases was included in previous analyses (European Collaborative Study, 1994).

Data analysis

We computed the vertical HIV transmission rate per calendar year from 1988 to 1995, using the number of infected children as numerator and the total number of children with known infection status as denominator.

To take account in the analysis of temporal trends in vertical HIV transmission rates, changes in clinical characteristics and mode of delivery, rates were directly standardized according to CD4+ count (<400, $\geqslant 400$), gestational age at delivery (<37, $\geqslant 37$ weeks), and mode of delivery (vaginal delivery or Caesarean section), taking the population of 1988 as reference.

To analyse details of the risk of HIV vertical transmission, we computed the odds ratios (OR) of the association between several factors and the infant's HIV serological status, together with their 95% approximate confidence intervals (CI), by the Mantel–Haenszel procedure (Mantel and Haenszel, 1959). When a factor could be classified in more than two levels, the statistical significance of the association was assessed by the χ^2 test for trend (Mantel, 1963). To account simultaneously for the effects of several potential confounding factors, we used unconditional multiple logistic regression, with maximum likelihood fitting, to obtain OR and their corresponding 95% CI (Breslow and Day, 1980). Included in the regression were terms for the factors significantly associated with the risk of mother-to-child HIV infection in age-adjusted analysis conducted considering the whole data set.

We also computed the proportion of HIV infected children attributable to factors statistically associated with the risk of mother-to-child infection. The attributable risk percentage (aetiological fraction, attributable fraction), representing the proportion of infected children in this study that would not have occurred if the effect(s) associated with the risk factor(s) of interest was/were absent, is a useful measure of public health and prevention relevance. The attributable risk for any given set of risk factors can be computed using the multivariate relative risk estimates and the distribution of these factors among HIV infected children only.

Thus, using the multivariate relative risks, population attributable risks were computed for each separate factor, and the factors combined, using the method described by Bruzzi *et al*. (1985), which provides a summary attributable risk (AR) for multiple factors, after allowance for confounding. The method requires information only on the joint distribution of the risk factors among infected children and on the adjusted OR associated with each risk factor. Provided that unbiased OR estimates are obtained and that the infected children can be assumed to be representative of all cases in the population in terms of exposure distribution, this method can be applied. It has to be noted that, whenever risk factors are not mutually exclusive, their combined attributable risk will differ from the simple sum of the attributable risks of each factor.

Table I. Frequency of HIV infected and uninfected children born in 13 obstetric departments in Italy, 1988–1995 calendar year. Italy 1988–1995

Calendar year	Infected No. (% of total no.)	Non-infected No.
1988	16 (15.7)	86
1989	21 (17.6)	98
1990	23 (17.4)	109
1991	23 (18.8)	99
1992	17 (14.4)	101
1993	16 (13.6)	102
1994	10 (13.3)	65
1995[a]	6 (9.7)	56

[a]Data from January to June.

Results

Table I shows the HIV mother-to-child transmission rate according to calendar year. Rates were highest in the period 1988–1991, then tended to decrease, and in 1995 the rate was 9.7 per 100 children (a finding based on only six infected children). This trend, however, was not statistically significant.

In order to analyse determinants of vertical HIV infection rates in different calendar periods, we analysed the potential risk factors for mother-to-child HIV transmission in the overall series and in strata of the quadrennia 1988–1991 (transmission rate of 17.5/100 children) and 1992–1995 (13.1/100 children).

The distribution of maternal characteristics according to infection status of the children and calendar year is considered in Table II. Considering the overall series, the risk of HIV vertical transmission was higher in women with low CD4 count in pregnancy (OR <400, versus $\geqslant 400$ 1.8, 95% CI 1.1–2.9). Similar findings emerged when the analysis was conducted in strata of the two quadrennia.

Table III considers obstetric factors and risk of vertical HIV transmission. The mode of delivery and gestational age at birth were associated with the risk of vertical transmission. In comparison with vaginal delivery, the risk of transmission was 0.3 (95% CI 0.1–0.5) and 0.6 (95% CI 0.3–1.2) respectively for elective and emergency delivery. The estimated OR tended to be lower in the calendar period 1992–1995, with estimated OR of respectively 0.4 and 0.2 for elective Caesarean delivery in the period 1988–1991 and 1992–1995 and 0.9 and 0.3 for emergency delivery.

In comparison with women who delivered at term ($\geqslant 37$ gestation weeks), the OR of HIV infection of the babies for the whole series was 2.2 (95% CI 1.3–3.6) in women who delivered preterm; the estimated OR were 1.6 (95% CI 0.8–3.0) and 3.4 (95% CI 1.5–7.8) respectively for the periods 1988–1991 and 1992–1995. No association emerged between

Table II. Distribution, and corresponding odds ratios, of HIV infected and uninfected children according to selected maternal characteristics and calendar period, Italy 1988–1995

	Total	1988–1991		1992–1995	
		No. infected (%) Total	OR (95% CI)	No. infected (%) Total	OR (95% CI)
Risk group					
Intravenous drug use		49 (14.8):332	[a]	29 (13.3):218	[b]
Heterosexual transmission		22 (24.7):89	–	12 (12.9):93	–
Other or unknown		12 (22.2):54	–	8 (12.9):62	–
Maternal age (years)					
<30	1+	66 (17.0):388	1+	27 (11.3):238	1+
⩾30	1.2 (0.8–1.9)	16 (21.1):76	1.3 (0.7–2.4)	20 (16.4):122	1.3 (0.7–2.5)
Zidovudine use in pregnancy					
No	1+	80 (17.5):457	1+	44 (13.5):326	1+
Yes	0.7 (0.3–1.4)	3 (16.7):18	0.8 (0.2–3.2)	5 (10.6):47	0.6 (0.2–1.7)
CD4+ count					
⩾400	1+	34 (13.9):245	1+	12 (10.3):116	1+
<400	1.8 (1.1–2.9)	35 (24.0):146	1.9 (1.1–3.3)	16 (16.8):95	1.7 (0.7–4.2)
Antigenaemia p 24					
Negative	1+	55 (17.0):323	1+	21 (11.9):176	1+
Positive	1.7 (0.9–3.1)	13 (27.7):47	1.7 (0.8–3.5)	6 (23.1):26	1.9 (0.6–5.8)
Intravenous drug use in pregnancy					
No	1+	68 (16.8):404	1+	38 (13.4):284	1+
Yes	1.2 (0.7–1.9)	15 (21.4):70	1.4 (0.7–2.8)	10 (13.2):76	1.0 (0.5–2.4)

OR = odds ratios. CI= confidence interval. Multivariate estimates including terms for age, CD4+ count, antigenaemia, mode of delivery and gestational age.
+ Reference category.
[a]χ^2 = 0.056.
[b]χ^2 = 0.994.

Table III. Distribution, and corresponding odds ratios, of HIV infected and uninfected children according to obstetric factors and calendar period, Italy 1988–1995

	Total	1988–1991		1992–1995	
		No. infected (%) Total	OR (95% CI)	No. infected (%) Total	OR (95% CI)
Mode of delivery					
Vaginal	1+	67 (19.2):349	1+	42 (17.7):238	1+
Caesarean	0.3 (0.2–0.6)		0.5 (0.3–0.9)		0.2 (0.1–0.4)
elective	0.3 (0.1–0.5)	9 (9.7):93	0.4 (0.2–0.8)	4 (4.4):92	0.2 (0.0–0.4)
emergency	0.6 (0.3–1.2)	7 (21.2):33	0.9 (0.4–2.4)	3 (7.0):43	0.3 (0.1–1.0)
Gestational age at birth (weeks)					
⩾37	1+	66 (16.4):402	1+	36 (11.7):309	1+
<37	2.2 (1.3–3.6)	17 (23.6):72	1.6 (0.8–3.0)	12 (21.1):57	3.4 (1.5–7.8)
Birth weight (g)					
⩾3000	1+	38 (15.8):241	1+	28 (14.0):200	1+
<3000	1.0 (0.7–1.6)	45 (19.5):231	1.3 (0.7–2.1)	20 (12.1):165	0.7 (0.3–1.5)
*Interval between rupture membranes and delivery (h)**					
<4	1+	8 (25.8):31	1+	23 (15.8):146	1+
⩾4	1.0 (0.5–2.1)	1 (10.0):10	0.3 (0.0–2.9)	14 (19.7):71	1.2 (0.5–2.6)

*Data not collected since late 1991.

infection status of newborn and birth weight (after taking into account the role of gestational week at birth) or the interval between rupture of membranes and delivery among women who delivered vaginally.

In the analysis of temporal trends in vertical HIV transmission rates, we computed standardized rates for all the factors found to be significantly associated with the risk of HIV vertical transmission in both calendar periods (Table IV). The frequency of Caesarean section increased from 26.5% in 1988–1991 to 36.2% in 1992–1995. Consequently, most temporal differences disappeared after standardization for mode of delivery, but the rate in 1995 was still lower than in 1988–1994. No difference was observed between crude rates and rates standardized for CD4+ count, and gestational age at birth.

We computed the proportion of HIV infected children attributable to the factors found to be significantly associated with vertical transmission. Since interaction terms were not significant, their coefficient were not included in the attributable risks presented. The 16% of HIV infected children could be attributable, during the whole study period, to pregnancy in

Table IV. Standardized[a] HIV vertical transmission rate/100 children per calendar year, Italy, 1988–1995

Year	Rate/100 children standardized for		
	Mode of delivery	CD4+ count	Gestational age at birth (rates)
1988	15.7	15.7	15.7
1989	17.3	18.8	17.7
1990	17.7	17.3	17.0
1991	19.0	19.7	18.8
1992	14.5	13.0	12.7
1993	15.1	14.8	13.7
1994	16.0	16.2	13.6
1995+	10.8	11.5	10.6

+Data from January to June.
[a]Standardized according to the direct method using the 1988 population as standard.

Table V. Attributable risk of vertical HIV transmission in relation to selected determinants and their combination, 1988–1995

Risk factor	Attributable risk %
CD4+ count <400	16
Vaginal delivery	54
Preterm birth (<37 weeks gestation)	12

women with low CD4+ count, the corresponding figures for vaginal delivery and preterm birth being 54% and 12% (Table V).

Discussion

The results of this study show that in Italy, the frequency of vertical HIV infection tended to decline from 1988 to 1995. This may have been due to the higher frequency of Caesarean section in the quadrennium 1992–1995. The main determinants of infection were preterm birth, mode of delivery and low CD4+ count, and did not change during the study period. No association emerged between the risk of vertical HIV transmission and maternal age, intravenous drug use in pregnancy, zidovudine in pregnancy, birth weight and time of rupture of the membranes.

The potential limitations of the study should be considered. This is an analysis of time trends and determinants of HIV vertical transmission in women of only one country. We think however that it is interesting to analyse in detail data from a specific country, in consideration of the more similar epidemiological characteristics of women considered and modalities of assistance to pregnancy. A large proportion of cases analysed in this paper have already been included in previous publications (European Collaborative Study, 1994). This analysis is focused however on some aspects (for example, the analysis of attributable risks) not presented in previous published papers. Although the study included ~1000 HIV infected mothers, it had low statistical power to identify an increase in the risk of vertical HIV transmission of two or more for factors with a prevalence lower than 30% in the study population. The proportion of missing data was generally limited, and there is no reason to think that infant HIV status is associated with the probability of missing data, since data were collected at delivery.

Information was limited on the role of zidovudine in reducing vertical HIV transmission (only 71 women reported zidovudine use in pregnancy in 1992–1995) and should be interpreted cautiously, since the drug was not given at random. However, the estimated OR of vertical HIV infection related with zidovudine use in pregnancy did not change after taking account of potential covariates of the treatment, i.e. CD4 levels and modalities of HIV infection in the mother. With these limitations, however, we did not find any association between zidovudine use in pregnancy and risk of vertical HIV-1 transmission. Similar findings emerged from a study with similar general design conducted in the USA between 1989 and 1994 (Landesman *et al*., 1996). These are not consistent with findings from a large clinical trial conducted in the USA showing a marked reduction of HIV infection among infants born to women treated with zidovudine (Connor *et al*., 1994). Results from non-randomized studies must be considered cautiously, and neither our data nor the American study indicate for how long treatment was given during pregnancy and whether women had received the drug before pregnancy and the infants were treated after birth. Further, it is possible that some confounding factors can explain the lack of association between ziduvudine in pregnancy and risk of vertical HIV-1 transmission. Along this line, it should be considered that in this series only a small proportion of women were treated with ziduvudine in pregnancy.

There is consistent evidence that low CD4+ levels are associated with an increased risk of vertical HIV transmission. For example, in the American Women and Infants Transmission Study, the risk of mother-to-child HIV transmission was about double in mothers with CD4+ cells <29% compared to those with ⩾29% (Landesman *et al*., 1996). Other studies in European and African populations (Ryder *et al*., 1989; St Louis *et al*., 1993; European Collaborative Study, 1996) gave similar results. Few data are available on how blood antigen levels affect the risk of HIV vertical transmission.

Analysis of the Collaborative European Study (including about 570 of the women considered in the present paper) suggested that Caesarean section may reduce the risk of HIV-1 vertical transmission (European Collaborative Study, 1994). A meta-analysis including data from 11 studies and about 3200 cases indicated that the reduction associated with Caesarean section amounted to ~20% (Dunn *et al*., 1994). However, the Women and Infants Transmission Study conducted in the USA (Landesman *et al*., 1996) and French perinatal cohorts (Mandelbrot *et al*., 1996) did not confirm these data.

In this study, the estimated OR for vertical HIV transmission was 0.3 in women who delivered by Caesarean section in comparison with those who delivered vaginally, confirming the protective effect. The consistency of the protection in different calendar periods gives some strength to this association. The higher proportion of Caesarean sections in the period 1992–1995 in comparison with 1988–1991 partly explains the lower vertical transmission rates in recent years. In fact, the

standardized rate of vertical transmission for mode of delivery was similar for all periods considered.

The association between low birth weight and mother-to-child infection has been analysed in several studies, but the results are conflicting (Lepage *et al*., 1993; Nair *et al*., 1993; Monfenson, 1994; Abrams *et al*., 1995). At least two American and African studies have shown an increased risk for low birth weight infants, but others did not confirm this. The association between low birth weight and vertical HIV transmission, may possibly be explained by the confounding effect of intravenous drug use in pregnancy, which is associated both with low birth weight and HIV vertical transmission or a more advanced stage of HIV infection in the mother. We did not find any association between birth weight and risk of mother-to-child HIV infection. However, we did find an association between preterm birth and risk of vertical HIV transmission. A similar association was seen in the Women and Infants Transmission Study and Prenatal cohorts (Landesman *et al*., 1996), but no association emerged between gestational age and risk of vertical HIV transmission in other studies (Ryder *et al*., 1989; Bucceri *et al*., 1997).

A USA study (Landesman *et al*., 1996) suggested that when the duration of ruptured membranes is 4 h or more, mother-to-child HIV-1 transmission increases by ~5% and the risk of vertical transmission tends to rise with the time of ruptured membranes. In this study, we only had information on the duration of ruptured membranes for the period 1992–1995, but we did not find any association with risk of HIV vertical transmission.

Finally, with regard to the proportion of HIV infected children attributable to the various factors, ~10% of infected children are attributable to preterm birth, a factor not preventable, but ~50% of HIV infected children were preventable by Caesarean section.

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