Higher In Utero and Perinatal HIV Infection Risk in Girls Than Boys

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Objective: This study analyzed mother-to-child HIV transmission rates by sex and exposure time for babies born to HIV-infected, untreated African women.

Methods: Data were analyzed from 2 independent studies done in Malawi during the 1990s. Infections were established by polymerase chain reaction on blood samples. Odds ratios (ORs) for transmission were examined by period at risk: in utero (infected in umbilical cord blood), perinatal (infected in 1st postnatal blood ≥4 weeks), and postnatal (later postnatal infection).

Results: Among 1394 singleton births, girls were more likely to become infected than boys. For in utero transmission, the OR was 1.4 (95% CI: 0.9 to 2.2). For transmission during early life (umbilical cord blood not available) the OR was 2.7 (95% CI: 1.5 to 4.9). However, transmission risks in the perinatal and postnatal infection periods did not differ in boys and girls. Among 303 tested twin-birth pairs, girls were at higher risk than boys for in utero (OR: 2.6; 95% CI: 1.2 to 5.8) and perinatal (OR: 1.9; 95% CI: 1.0 to 3.7) infection. Recognized mother-to-child transmission risk factors did not explain the higher risk of infection in girls.

Conclusions: Girls were at higher risk of early (in utero and perinatal) HIV infection than boys. It is proposed that minor histocompatibility reactions between maternal lymphocytes and infant Y chromosome–derived antigens reduce the risk of HIV transmission in boys.

Key Words: vertical transmission, gender, infants, female, male, retrovirus, HLA

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Among infants born to HIV-infected women, girls may be more likely to become infected than boys. In a study of mother-to-child HIV infection risk of 3231 non–breast-fed infants born to European women between 1986–2003, girls had a significantly higher risk of "early" infection (time unknown) than boys (odds ratio [OR] 1.49; 95% CI: 1.04 to 2.13). Adjustment for maternal and infant variables known to affect transmission risk, including maternal viral levels and delivery factors, did not change this association.[1] Similarly, among 1954 infants born to HIV-infected mothers in Malawi, girls were more likely to be infected than boys.[2] The ORs were 2.14 (95% CI: 1.56 to 2.95) for in utero infection and 1.39 (95% CI: 0.97 to 1.99) for perinatal infection. Again, adjusting for known transmission risk factors did not affect the ORs greatly. In an earlier study done in Cote d'Ivoire, investigators also reported that significantly more girls (63%) were infected than boys (34%), but that study was limited to 79 malnourished infants.[3]

From these studies, it appears that girls may be more susceptible to HIV infection. However, why girls and boys may have different susceptibilities is still puzzling. Furthermore, investigators of mother-to-child HIV transmission treatment trials have not reported infants' sex to be significantly associated with transmission risk.[4,5] These studies had relatively few infected infants and did not differentiate in utero vs. perinatal risk. Finally, in a result that seems to conflict with the hypothesis of greater susceptibility of girls, a recently published meta-analysis reported that boys were at significantly greater risk of infection via breast-feeding than girls.[6] Those investigators also stated that earlier infection risk was not associated with the infants' sex ($P = 0.24$) but did not provide further details.[6]

To investigate the possible difference in susceptibility to HIV infection by sex, we analyzed data from 2 independent studies of mother-to-infant HIV transmission done in Malawi.[7,8] In this report, we confirm that girls are more susceptible to infection, especially in utero. We also offer a hypothesis for why transmission risk differs by sex and why this difference is most prominent for infections occurring in utero.

METHODS

In 1994, we conducted a large intervention trial at Queen Elizabeth Central Hospital in Blantyre, Malawi to study the efficacy of vaginal cleansing with an antiseptic, chlorhexidine, during labor to reduce HIV transmission from infected mothers to infants. The intervention had no impact on the risk of HIV transmission to the infant,[7] although it did provide impressive reductions in the risk of bacterial

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infections for both mothers and infants.[9] As a follow-up to that study, we conducted a study of the HIV infection risk of live-born infants delivered as multiple births at this hospital between 1996 and 2003.[8] No interventions were given to the mother and infants because this study ended before antiretroviral therapies were introduced in Malawi in 2003. Our reanalysis of these 2 studies focuses on the infants' sex as a risk for infection, a variable not previously considered. Both studies were approved by ethical review boards at the participating institutions and enrolled only consenting mothers.

In both studies, live-born infants delivered during the study period were enrolled regardless of the HIV status of the mother. Data about the sex distribution of children lost to follow-up are presented to demonstrate that follow-up and testing of male and female infants were similar. Analysis of infection risk was restricted to HIV-infected women and their infants. For simplicity, analyses of the intervention trial were confined to singleton births. For analyses of multiple-birth infants, only the first 2 live births ("twins") were used (4 third live-births excluded). A child born in a twin pair was considered a twin birth even if only 1 child of a twin set was born alive, but matched-pair analyses included only sets in which both twin mates were live born and evaluated for infection during the specified period of exposure (in utero or perinatal). Follow-up in twin pairs was poor because recognized twin pregnancies (high risk) were referred to our tertiary care hospital from outlying clinics, often quite distant, and because infant mortality in twin-born infants was high. Many twin-born infants had no or only 1 postnatal visit. Thus, data on breast-feeding infection risk for twins were incomplete and are not presented.

HIV infection was established by polymerase chain reaction (PCR) for HIV genome using blood samples collected on filter paper.[10] Infants were considered to be infected in utero if HIV was detected by PCR done on umbilical cord blood. These infants must have been infected in utero because cord blood HIV levels were almost all as high as or higher than those in their mothers.[11] Infants who were PCR negative at birth and PCR positive on their first postnatal visit (4–26 weeks; mean 7 weeks) were considered to have been infected perinatally. These infections were assumed to have occurred during delivery (point source), in accord with our previous publications,[7,8,10–12] but a few may have occurred during the early weeks of breast-feeding. Infants who were HIV negative on their first postnatal PCR done after 4 weeks were considered at risk for breast-feeding infection. Follow-up in the breast-feeding analysis was truncated at infection, at the end of breast-feeding, or at the time last tested, whichever came first. Infection risks were analyzed separately for in utero, perinatal, and postnatal infections. Additionally, an "early" infection risk was determined for children who lacked HIV status in cord blood but who had an early HIV result (by 26 weeks), consistent with the European study.[1]

Fisher exact and χ^2 tests, as appropriate, were used for probability values (2-sided $P < 0.05$ considered statistically significant). ORs with 95% CIs were used for comparisons. Comparisons in twins were done for all twin births and paired analyses were done for twin pairs using the general estimator equation (PROC GENMOD; SAS, Cary, NC), in which the mother was used as a "class" to adjust for variation in her infectiousness. For opposite-sex twin pairs in which only 1 infant was infected, we used the McNemar test. Risks of infection by breast-feeding in singletons were analyzed by Kaplan–Meier curves and assessed by the Cox proportional hazard model (log-rank test).

For both data sets, we also fit models that included established risk factors for HIV mother-to-child transmission risk. These risk factors included delivery route, birth weight as a measure of prematurity, Apgar score (1 minute) as a measure of delivery stress, duration of rupture of membranes and labor, and mother's age and parity. Associations between these variables and HIV transmission risk have been previously described[7,8] and are therefore presented only briefly. The intention of these analyses was to determine whether the distribution of risk factors differed by the sex of the infant and could possibly be confounders or effect modifiers for HIV transmission to girls or boys. Maternal HIV levels and measures of immunity were not done in either of our studies, but in other studies they have not differed significantly in mothers of girls and boys.[1,2] In twins, analysis by birth order is included. In twin births we did not have definitive information about their identical- vs. fraternal-twin status. Because feto–fetal transmission between identical twins could have influenced concordance, we examined transmission in same-and opposite-sex (which must be fraternal) twin pairs.

RESULTS

Singleton-Birth Comparisons

Table 1 presents results on 4698 babies born to HIV-uninfected women and 2032 babies (30.2%) born to HIV-infected women. The proportion of girls was the same in both groups (50.1% each). Of babies born to HIV-infected women, 1394 (704 girls and 690 boys) were HIV tested. By Kaplan–Meier estimation, at 12.0 months of age, the proportion infected by any route (28.1%) was typical of that expected in Malawi in the mid-1990s, when treatment was not available,[7] but it was slightly higher in girls (27.8%) than boys (24.6%). Only children not infected in an earlier period were at risk for infection during a subsequent evaluation period, and there were additional losses from death or lack of follow-up, resulting in progressively smaller numbers for evaluation in each specific transmission period.

Established in utero infections occurred in 53 (9.6%) of 553 girls tested at birth, compared with 39 (7.1%) of 549 boys (OR: 1.4; 95% CI: 0.9 to 2.2). For 292 infants, cord blood results were not available, but HIV test results were available at 4–26 weeks (median: 7 weeks; interquartile range: 6–8 weeks), permitting assessment of "early" infection risk (in utero or perinatal infection). In this group, 52 (34.4%) of 151 girls and 23 (16.3%) of 141 boys were infected (OR for "early" infection: 2.7; 95% CI: 1.5 to 4.9). Among 893 infants not infected in utero, perinatal infection risks were similar in girls and boys (OR: 0.9; 95% CI: 0.6 to 1.2). Among infants not infected at the first postnatal test at ≥4 weeks, later results were available on 639 infants. Breast-feeding infections were

TABLE 1. HIV Infection in Singleton-Birth Infants in Malawi, by Sex

	Girls		Boys		Total
Mother HIV uninfected	2356 (50.1%)		2342 (49.9%)		4698
Mother HIV infected	1018 (50.1%)		1014 (49.9%)		2032
Infant HIV tested*	704 (50.5%)		690 (49.5%)		1394
	Tested	**Infected**	**Tested**	**Infected**	**OR (95% CI)**
"Early" infection†	151	52 (34.4%)	141	23 (16.3%)	2.7 (1.5 to 4.9)
In utero infection	553	53 (9.6%)	549	39 (7.1%)	1.4 (0.9 to 2.2)
Perinatal infection	443	73 (16.9%)	450	88 (19.6%)	0.9 (0.6 to 1.2)
Breast-feeding infection‡	318	22 (6.9%)	321	18 (5.6%)	Cox $P = 0.52$

*Testing done at least once during the study period. Only infants not infected at an earlier time remained at risk for infection during a later interval.
†Umbilical cord blood not obtained but postnatal results available.
‡Point estimate at 18 months; Cox *P* based on Kaplan–Meier assessment.

observed in 22 (6.9%) of 318 girls and 18 (5.6%) of 321 boys. At age 18 months, the Kaplan–Meier estimates of breast-feeding infection risk were 3.2% for girls and 2.6% for boys (Cox test for life table test for relative hazards $P = 0.52$).

We conducted a detailed analysis of risk factors that might have affected transmission. The distributions of mother's age, parity, duration of rupture of membranes or labor, route of delivery (operative or vaginal), Apgar score, and birth weight were not significantly different whether the child was a girl or boy (all $P > 0.20$). None of these factors greatly altered the OR of in utero HIV infections for girls vs. boys (data not shown).

Twin-Birth Comparisons

In twin births (Table 2), 1587 infants were born to HIV-uninfected mothers and 690 infants (30.3%) were born to HIV-infected mothers. The proportions of girls were similar in each group (49.5% and 50.4%, respectively; $P = 0.67$). Umbilical cord blood HIV status was missing on 35 boys and 37 girls (excluded). In 12 twin pairs, only 1 infant was tested (none infected), because the twin mate was born dead (excluded). In utero infection occurred in 27 (8.9%) of 302 girls, compared with 11 (3.6%) of 304 boys (matched-pair analysis, OR: 2.5; 95% CI: 1.3 to 3.3). The proportion of twin births without follow-up testing did not differ significantly between girls (37.3%) and boys (41.6%) ($P = 0.30$). Of all twin pairs not infected in utero and evaluated for perinatal infection, infections occurred in 28 (18.1%) of 155 girls and 15 (9.7%) of 155 boys (matched pair OR: 1.8; 95% CI: 1.0 to 3.5). Not surprisingly, twin mates were significantly likely to be concordant in infection status, a finding previously published from this data set[8] and also seen here. Adjusting for birth order and same-or opposite-sex twin pairs, the ORs were little changed and remained significant (Table 3). In a small subset of sex-discordant twin pairs with only 1 infected child, twin mates were exactly matched for in utero exposure to their mother. In these sex-discordant pairs, 7 girls and 1 boy were infected in utero (88% girls; exact CI: 47% to 100%) and 5 girls and 3 boys were infected perinatally (62% girls; exact CI: 24% to 91%).

In analyses of other risk factors that might have affected perinatal infection in twins, the factors identified were generally similar to those of singletons, as previously presented.[8] However, the distribution of these risk factors did not differ significantly between girls and boys, and extensive analyses yielded no suggestion of confounding or effect modification by these variables (data not shown). Cesarean delivery was strongly protective for perinatal ($P = 0.02$) but not in utero infection risk ($P = 0.39$). In a model

TABLE 2. HIV Infection in Twin-Born Children in Malawi, by Sex

	Girls		Boys		Total
Mother HIV negative	785 (49.5%)		802 (50.5%)		1587
Mother HIV positive	348 (50.4%)		342 (49.6%)		690
Infant HIV tested*	311 (50.3%)		307 (49.7%)		618
Both infants of pair tested	302 (49.8%)		304 (50.2%)		606
	Tested	**Infected**	**Tested**	**Infected**	**OR (95% CI)**
In utero infection	302	27 (8.9%)	304	11 (3.6%)	2.5 (1.3 to 3.3)†
Perinatal infection	155	28 (18.1%)	155	15 (9.7%)	1.8 (1.0 to 3.5)†
Breast-feeding infection			Not presented‡		

*Testing done at least once during the study period. Only infants not infected at an earlier time remain at risk for infection during a later interval.
†ORs and CIs from twin pairs analyzed by matched-pair analysis done when both members of the twin pair were still at risk of infection.
‡Too few twin pairs had sufficient postnatal follow-up to provide reliable results.

TABLE 3. In Utero and Perinatal HIV-1 Infections in Twin Pairs Born to HIV-1–Infected Women When the Infection Status of Both Twin Mates Was Known, by Birth Order and Sex

	Birth Order and Sex												
	1st Boy	2nd Boy	#	1st Girl	2nd Girl	#	1st Boy	2nd Girl	#	1st Girl	2nd Boy	#	1st 2nd Total
In utero infection	+	+	2	+	+	3	+	+	3	+	+	1	9++
	+	−	1	+	−	8	+	−	0	+	−	2	11+−
	−	+	1	−	+	2	−	+	5	−	+	1	9−+
	−	−	87	−	−	77	−	−	59	−	−	51	274−−
Total			91			90			67			55	303
Perinatal infection*	+	+	1	+	+	4	+	+	1	+	+	3	9++
	+	−	4	+	−	3	+	−	1	+	−	3	11+−
	−	+	2	−	+	8	−	+	2	−	+	2	14−+
	−	−	38	−	−	30	−	−	32	−	−	21	121−−
Total			45			45			36			29	155

*Among twin pairs when neither was infected in utero.
+ indicates infected; −, uninfected.

including mode of delivery, girls remained at higher risk of perinatal infection than boys (OR: 1.8; 95% CI: 0.94 to 3.3).

DISCUSSION

In the current study, we found girls to have a higher risk of in utero and perinatal HIV infection than boys, which agrees with earlier studies.[1–3] In twin births, the ORs for girls compared with boys (in utero OR: 2.5; perinatal OR: 1.8) were similar to previous reports. In singletons, the OR for "early infection" risk (no cord blood tested) was 2.7, and the OR for in utero infection risk was 1.4. However, perinatal and breast-feeding infection risks were similar in girls and boys. Adjustments for other risk factor variables did not explain the findings of a higher infection risk in girls in either twins or singletons. We had no data about the viral levels or immunity of the mothers, but in other studies[1,2] mothers of girls and boys did not differ in these parameters. Finally, having the same mother, sex-discordant twin mates had identical in utero exposures to both known and unknown maternal parameters, but when only 1 of the 2 children was infected, it was more likely to be the girl (7 girls and 1 boy). Thus, in agreement with 2 other large studies,[1,2] the preponderance of our data showed a greater risk of infection in girls compared with boys, especially when infection occurred in utero.

The excess infection risk in girls was most pronounced for in utero infections and therefore could not be attributed to follow-up differences by sex. We excluded this possibility for perinatal infection by showing that follow-up was similar for girls and boys, but the excess infection risk in girls persisted into the perinatal infection period, albeit at a lower differentials. However, these studies enrolled only live-born infants. Therefore, the excess risk in girls theoretically could have been due to better in utero survival of HIV-infected girls than boys. There are no records about the sex distribution of fetal losses in Malawi. In developed countries, in utero death rates (all-cause) are higher in boys than girls, but more boys than girls are conceived as well, so that about 51.5% of live births are boys.[12] The proportion of boys in our Malawi studies, 49.9% in singletons and 50.2% in twins, was slightly lower than in developed countries, but the proportion of infants born boys was similar in HIV-negative and HIV-positive women. Although we think it is unlikely, we could not exclude off-setting risks in which more boys than girls were HIV infected in utero but more infected boys than girls also died in utero. Against this possibility, the same proportion of girls and boys born to HIV-infected women had follow-up visits, indicating that neonatal losses of infected girls and boys were similar, and that, in the perinatal period, girls also were more likely to become HIV infected than boys. We therefore sought a biologic explanation for why girls might be at higher risk of mother-to-child HIV infection than boys.

In utero and delivery-related HIV infections probably occur mainly because of microtransfusions of infected maternal lymphocytes across the placenta.[7] In 1998, MacDonald et al[13] observed that infants were more likely to become HIV infected when they shared class I HLA type concordance with their mothers. This finding was subsequently confirmed elsewhere.[14] These HLA associations implied that immunologically mediated mechanisms affected HIV infection risk. The investigators speculated that microtransfused maternal cells survived longer when they were more HLA concordant with those of the infants and thereby were more likely to establish HIV infection in the infant. We did not have HLA types in our studies, but the distribution of HLA type concordance between mother and infant would not be expected to differ in boys and girls because the HLA genes are on chromosome 6, not a sex chromosome.

In parallel with the HLA hypothesis, we propose that H-Y–derived antigens on the cells of boys serve as additional recognition markers for immune reactions occurring between cells of the mother and infant. If correct, this H-Y incompatibility hypothesis has an important implication for the direction of the immune reaction. Male cells contain an X chromosome acquired from the mother and therefore would not recognize X chromosome–derived antigens on the mother's cells as foreign. However, the maternal lymphocytes would recognition Y chromosome–derived

antigens of boys as foreign. Female cells react to Y chromosome–derived antigens in ways that are clinically significant. In 1975, Uphoff[15] noted that graft-vs.-host disease in inbred mice was more common when female donor bone marrow was placed into males than when same-sex marrow was used. Similarly, in humans, graft-vs.-host reactions were also more common and mortality rates higher when males received female donor cells than in sex-matched sibling donor–recipient pairs, even when these pairs were HLA identical.[16–18] The mechanism of the adverse outcome for males receiving sex-mismatched transplantation is now recognized to be related to antigens from the Y chromosomes that provoke histocompatibility reactions initiated by female donor $CD4^+$cells.[19]

Maternal lymphocyte reactions to Y chromosome–derived antigens could reduce infection risk for boys in at least 2 ways. The HIV-infected maternal lymphocytes activated by Y chromosome–derived antigens could release cytokines that have been shown to block HIV infection or inhibit HIV replication, such as RNase eosinophil-derived neurotoxin from the eosinophil-derived neurotoxin superfamily[20] or other alloantigen-stimulated factors.[21] Alternatively, H-Y incompatibility could operate by shortening maternal lymphocyte survival in boys through maternal lymphocyte antigen–induced cell death. We note that these mechanisms could also explain the inverse association between mother-to-child transmission risk and HLA concordance, if infection risk in the HLA context is affected more by mother-against-child reactions than by the postulated child-against-mother immunologic reactions. These possibilities should be amenable to in vitro study and deserve further consideration. Clearly, however, boys can be infected at any time pre- or postnatally, and therefore the protection provided by the H-Y incompatibility with maternal lymphocytes is limited.

In the current studies and others,[1,2] the excess risk of infection in girls has been consistently more pronounced for in utero infection than perinatal infection. Our hypothesized role for H-Y immunity applies specifically to reducing infection from HIV-infected cells, such as might occur from transplacental passage of infected maternal cells. This route would be likely for in utero infection, but for infections occurring at or after delivery, free virus may play a more important role. Infections resulting from free virus would not be susceptible to the same cellular immune mechanisms we postulate, resulting in less difference in the perinatal infection risk for girls and boys. Finally, in breast-feeding HIV infections, free virus may play a dominant role, resulting in a similar infection risk in girls and boys. Although this hypothesis does not explain the excess risk for boys reported in the meta-analysis of breast-feeding data,[6] we were unable to confirm this observation, finding instead that boys and girls were equally at risk for infection by breast-feeding.

In summary, our findings confirm previous reports that girls have a greater risk of in utero and, to a lesser extent, perinatal HIV infection than boys. We propose that H-Y incompatibility cellular reactions occur when maternal cells are microtransfused into boys and provide supporting arguments that H-Y incompatibility reaction initiated by maternal cells could explain the excess risk of mother-to-child HIV transmission.

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