ORIGINAL ARTICLES

Maternal HIV infection, drug use, and growth of uninfected children in their first 3 years

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Abstract

Objective—To determine the separate effects of maternal HIV infection and drug use during pregnancy on growth of uninfected children in their first 3 years. *Design*—Retrospective analysis of measurements from health visitor records made during routine child health surveillance at 6 weeks, 10 months, and 3 years of age. Multilevel analysis allowed for between-infant variation in fitted growth lines, and adjustment for other factors. Growth was described in terms of an intercept (z score at term) and growth slopes (change in z score per year) up to, and from, 4 months.

Subjects—290 case babies delivered in Edinburgh hospitals to women who reported injection drug use by either themselves or their HIV infected partner, and 186 community controls. A total of 131 (45%) of the case babies were born to women who used drugs, predominantly opiates, during pregnancy and 93 (32%) to HIV infected women. The eight infected children were excluded from analysis.

Main outcome measures—Age and sex standardised z scores for height, weight, and body mass index.

Results—459 (96%) of the 476 records for cases and controls were traced, yielding 1432 weight and 939 height measurements. Maternal HIV infection was not found to affect growth; at 3 years the estimated effect on weight z score was 0·16 with 95% confidence interval (−0·25 to 0·57) and for height 0·18 (−0·19 to 0·55). Drug use during pregnancy was associated with lighter babies at 40 weeks followed by depressed growth in the first four months, these infants remaining just slightly smaller at 3 years with an estimated effect on z scores of −0·5 for weight with 95% confidence interval (−0·89 to −0·11) and −0·37 (−0·72 to −0·02) for height. *Conclusions*—Maternal HIV infection does not adversely affect growth in uninfected infants, and the effect of drug use during pregnancy is limited to small decrease in size at 3 years.

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During the early 1980s, HIV infection in Edinburgh women was largely associated with intravenous drug use either by the woman herself or her heterosexual partner. Opiate use during pregnancy is associated with lighter babies, even taking into account gestational age.[1] The subsequent pattern of growth in drug affected infants is less well established, due to difficulties in identifying and following up adequate numbers of cases and controls.[2] Some longitudinal studies report impaired postnatal growth,[3–6] and others do not[7–10] with a suggestion of reduced growth only in the first four to six months until withdrawal symptoms resolve.[11]

Maternal HIV infection may have an effect on birth weight. Reports from the developed world show no association, whereas most of the much larger studies from Africa show significantly decreased birth weight.[12] The in utero experience may be different and affect postnatal growth patterns. Additionally, maternal HIV infection also introduces stresses which may interfere with parenting: the mother's concerns, her partner's response to diagnosis, their poorer health which may expose the infant to other infections, and reactions from the community.

Studies in the US[13 14] and Europe[15 16] have documented the smaller size of infected compared with uninfected children born to HIV positive mothers, but a control group of uninfected mothers is necessary to investigate and compare the effects of maternal HIV infection on growth in uninfected children. The separate effects of maternal HIV infection and drug use on birth weight have been examined using cases and controls born in Edinburgh hospitals (F D Johnstone, *et al*, unpublished). This follow up study investigates the separate contributions of maternal HIV infection and drug use during pregnancy on both growth from birth to 3 years, and on size attained at 3 years.

Subjects and methods

HIV antibody testing became available in October 1985 and shortly after this the high prevalence of HIV in injecting drug users in Edinburgh was reported.[17 18] Since then women presenting for antenatal care have been specifically questioned about drug injection by

Table 1 Characteristics of babies and their mothers; values are number (%) except if otherwise stated

	Mother HIV positive (n=93)	Mother HIV negative (n=197)	Controls (n=186)
Babies infected with HIV	8 (9)	0	0
Drug use during pregnancy	43 (46)	88 (45)	0
Smoking during pregnancy (cigarettes/day)			
None	12 (13)	24 (12)	25 (13)
1–9	13 (14)	28 (14)	41 (22)
10–19	35 (38)	67 (34)	71 (38)
≥20	33 (35)	78 (40)	49 (26)
Parous	49 (53)	105 (53)	98 (53)
Deprivation score at time of birth			
≤3	7 (8)	30 (15)	16 (9)
4	40 (43)	65 (33)	75 (40)
5	7 (8)	28 (14)	18 (10)
6	16 (17)	29 (15)	26 (14)
7	23 (25)	45 (23)	51 (27)
Mean (SD) height (cm)	160·1 (6·1)	160·3 (6·0)	161·2 (6·0)
Mean (SD) age at delivery	23·6 (4·2)	23·5 (4·6)	23·8 (4·4)
Gestation under 37 weeks	14 (15)	31 (16)	24 (13)
No of males	35 (38)	115 (58)	96 (52)
No of twin individuals	6 (6)	2 (1)	12 (6)
Feeding*			
Formula	88 (98)	145 (81)	113 (68)
Breast	2 (2)	35 (19)	54 (32)
Not known	3	17	19

*Not known includes 17 with no completed forms. The percentages given are of those with known method of feeding. For analysis, they are imputed to be formula fed.

themselves or their partner. HIV testing was readily offered where there were risk features. In addition there has been wide availability and acceptance of HIV testing in a number of sites throughout the city. This policy has meant a fairly complete recognition of HIV infected women who became pregnant (personal communication, F Johnstone). The study database was built up from many sources, including the virus laboratories, the City Hospital HIV screening clinic, the antenatal clinic for drug users and HIV seropositive women, the City Hospital Infectious Diseases Unit, other hospital departments, the Community Paediatric Unit, and examination of all delivery ward and operating theatre records.

The cases were live births to women who had had an HIV test performed, and who reported either injecting drug use since 1982 or a drug using infected partner, or both, as risk factors. Two hundred and ninety infants born between February 1983 and November 1992 were enrolled, of whom 93 were born to HIV infected mothers, 19 of whom never injected. One hundred and thirty one (45%) of the mothers of the cases used drugs during pregnancy, and a further 93 (32%) were former intravenous users. Although polydrug use was common, and drug use patterns have changed considerably during the time interval, the predominant drugs were opiates. This involved mainly heroin and buprenorphine by injection, and oral methadone and dihydrocodeine as substitution. The mothers of 109 (38%) of the case infants were neither infected with HIV nor

reported drug use during pregnancy and 43 (15%) had both these features. All mothers were white and 253 (87%) of the babies were discharged to postcode sectors with deprivation scores of 4 or more on a scale from 1 to 7, 7 being the most deprived category.[19]

Each baby born to an HIV positive woman had two controls matched for parity (primiparous or parous), age (within 5 years), year of delivery, reported smoking during pregnancy (smoker or non-smoker), hospital (where possible), the same or an adjacent postcode deprivation score,[19] twin deliveries, and ethnic group. Selection of controls was performed by computer search for these multiple criteria using an area wide database (Information and Statistics Division, NHS in Scotland). Where several possible controls were identified, the first satisfactory match to be identified was chosen. None of the records of selected controls contained evidence of HIV testing or drug use in either the mother or her partner. One hundred and eighty six controls were entered into the study, giving a total of 476 babies.

Follow up was based on information collected during routine child health surveillance by health visitors in the child health records. These records remain with the health visitors until the child is of school age, when they are sent to the school nurse. The Child Health Information Systems for Lothian was searched for information on each child in the study; their health visitor, school, whether still resident in the Edinburgh area, adoption, and death. Between December 1992 and August 1994, 459 (96%) of the 476 health visitor records were traced. The remaining 17 children (4%) had left the area and their records were not located.

A form was designed to standardise the information to be extracted from these records concerning the child's growth and development. The forms were completed by one of two researchers (SG, BH), and included information on health care, family circumstances, developmental screening, method of feeding, and changes of address. Routine surveillance was scheduled for 6 weeks, 10 months, and 3 years of age. Measurements made on the visits closest to these dates and lying within predefined window periods 5–12 weeks, 7–18 months, and 2–4 years were recorded, together with the exact date of visit. Body mass index (BMI), weight (kg)/height (m)^2, was calculated for those with weight and height measurements made on the same visit. Hospital records provided information on the babies' measurements at birth, reported maternal smoking,

Table 2 Number of infants with recorded measurements by HIV status and visit, and as a percentage of the number of infants alive and old enough to have measurements taken when the form was completed; values are number (%)

|	Weights				Heights (lengths)			
	Baby infected (n=8)	Mother positive (n=85)	Mother negative (n=197)	Controls (n=186)	Baby infected (n=8)	Mother positive (n=85)	Mother negative (n=197)	Controls (n=186)
Total forms	8 (100)	84 (99)	193 (98)	174 (94)	8 (100)	84 (99)	193 (98)	174 (94)
At birth	8 (100)	84 (100)	193 (100)	174 (100)	7 (88)	71 (85)	161 (83)	115 (66)
6 Weeks	8 (100)	75 (89)	166 (86)	158 (91)	5 (63)	61 (73)	85 (44)	66 (38)
10 Months	6 (86)	75 (91)	142 (75)	133 (77)	5 (71)	66 (80)	82 (43)	78 (45)
3 Years	6 (100)	66 (85)	84 (49)	63 (40)	4 (67)	61 (78)	75 (44)	53 (34)
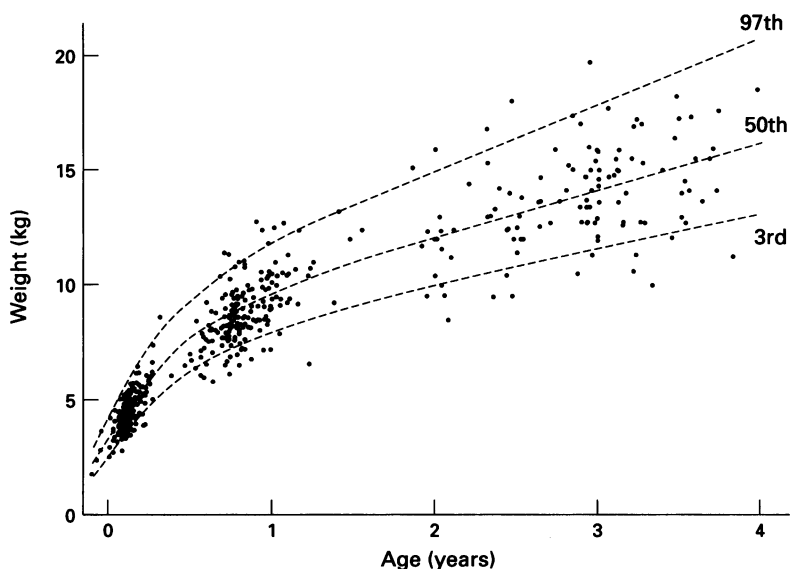
Figure 1   Data from 213 females plotted against the UK 3rd, 50th, and 97th centiles.

Table 3   Mean z scores by visit for the 451 HIV uninfected infants

	Weight z score		Height z score		BMI z score	
	No	Mean (SD)	No	Mean (SD)	No	Mean (SD)
Birth	451	−0·29 (1·0)	300	0·71 (1·4)	300	−1·54 (1·0)
6 Weeks	391	−0·15 (1·2)	209	0·20 (1·3)	206	−0·19 (0·9)
10 Months	349	−0·12 (1·3)	223	−0·09 (1·3)	220	0·13 (1·1)
3 Years	213	−0·03 (1·3)	186	−0·23 (1·2)	181	−0·08 (1·2)

drug use during the pregnancy, age, gestation, and mother's height measured in pregnancy.

STATISTICAL ANALYSIS

HIV infected children show delayed growth in relation to uninfected children born to positive mothers.[13–16] The eight infected infants in this study showed a retarded, different pattern of growth, and they are excluded from further analysis.

The remaining measurements were standardised for chronological age and sex into z scores using the 1990 UK growth standards.[20 21] Some mothers, particularly those using drugs, had shorter gestation times than were referenced in the growth standards. Birthweight standards covering a wider range of gestation period had been previously calculated from a series of over 19 000 Edinburgh births and could be used for the birthweight z scores (G Raab, personal communication). Where the gestation periods overlapped, the calculated z scores from the two standards were very similar. Z scores correspond directly to centiles, a child on the 50th centile having a z score of zero, and on the 95th centile a z score of 1·64. As the z score is a standardised

measure, z scores for boys and girls can be combined.

Separate analyses were carried out for weight, height, and BMI z scores using ML3 statistical software.[22] The growth patterns were analysed using a multilevel model which is similar to linear regression but recognises that the data consist of series of z scores from individual children and allows for variation between children in the fitted growth lines. This hierarchical approach extends to allow recognition of mothers who have more than one child entered into the study. Each child has an intercept representing his or her estimated z score at 40 weeks (regardless of gestation and so not strictly the z score at birth). Each child also has a slope representing his rate of growth in relation to the standards, where, for low birthweight babies, a positive slope suggests catch up growth and a negative slope indicates further growth retardation. A child lying on the 50th centile throughout his childhood would have z scores of zero for all his window measurements, and is represented by a horizontal line through z=0. As the assumption of a steady, linear rate of growth in relation to the standards may not be correct for low birthweight babies[23] or for babies exposed to drugs in utero,[11] the estimates of the growth slope were allowed to differ in the first months of infancy and later periods. Four months was chosen as this change point as it lies between the 6 week and 10 month window periods and had the best fit with the lowest residual error from models fitted with three, four, five, and six month time breaks. It is also a convenient break for adjusting for covariates such as method of feeding for which a pattern emerges[24 25] of heavier breast fed babies for the first 4 months after which the formula fed babies steadily overtake. The 4 month cut off allows investigation into the effects of maternal HIV infection and drug use on growth separately in the two time periods. Thus the growth slopes were estimated both up to, and from, 4 months.

The children's z scores were correlated, more so for pairs of visits with a shorter time gap and greater mean age. The correlation between the birth and 6 week weight z scores was 0·55 and between 6 weeks and 10 months was 0·53, with the strongest between 3 years and 10 months (0·77). The model allowed z scores at the different time points to have varying degrees of correlation.

The estimated effects of HIV infection and drug use during pregnancy on both size at 40 weeks and growth in both time periods can be adjusted for additional covariates. The jointly estimated effects of maternal HIV infection

Table 4   Estimated effects of maternal HIV infection on z score with 95% confidence interval

	Weight	Height	BMI
No of observations	1404	918	907
Size at 40 weeks	−0·17 (−0·42 to 0·08)	−0·33 (−0·69 to 0·04)	0·03 (−0·23 to 0·29)
Growth to 4 months	0·94 (−0·09 to 1·97)	1·30 (−0·24 to 2·85)	0·37 (−0·93 to 1·66)
Growth from 4 months	0·006 (−0·14 to 0·15)	0·03 (−0·14 to 0·20)	−0·06 (−0·25 to 0·12)
Size attained at 3 years	0·16 (−0·25 to 0·57)	0·18 (−0·19 to 0·55)	−0·02 (−0·44 to 0·40)

Adjusting for mother's height, age at delivery, smoking during pregnancy, postcode deprivation score, parity, method of feeding, twins, and case or control.

Table 5   Estimated effects of drug use in pregnancy on z score with 95% confidence interval

	Weight	Height	BMI
No of observations	1404	918	907
Size at 40 weeks	−0·22 (−0·44 to 0·00)*	0·06 (−0·27 to 0·38)	−0·40 (−0·63 to −0·16)*
Growth to 4 months	−0·30 (−1·27 to 0·67)	−1·46 (−2·92 to 0·01)	1·10 (−0·15 to 2·35)
Growth from 4 months	−0·07 (−0·10 to 0·21)	0·02 (−0·15 to 0·19)	−0·12 (−0·30 to 0·07)
Size attained at 3 years	−0·5 (−0·89 to −0·11)*	−0·37 (−0·72 to −0·02)*	−0·34 (−0·76 to 0·08)

Adjusting for mother's height, age at delivery, smoking during pregnancy, postcode deprivation score, parity, method of feeding, twins, and case or control. *$p<0.05$.

and drug use during pregnancy were adjusted for being a twin or control, postcode deprivation score, infant feeding (breast or formula fed at discharge), parity, maternal age, and smoking (0–9 or 10 or more cigarettes per day). The variables mother's height, deprivation score, and age at delivery were found to be approximately linearly related to z score for weight. Although much of the variation in children's heights can be accounted for by parental height,[26] unfortunately no data on the heights of the fathers were available. However, as mother's height predominates over father's height as a determinant of length at birth[27 28] and the association is not dissimilar for boys and girls at this age,[29] mother's height, as measured in pregnancy, was included as an intercept covariate in the model.

Results

The details of the 476 babies recruited into the study are given in table 1. Twelve mothers had three children, 52 had two, and the remaining 336 just one child enrolled in this study. Thirteen infants died before the age of 3; five were born to infected mothers, two of whom were themselves infected, six were born to uninfected case mothers, and three were controls. Six of these infants were born to mothers using drugs during pregnancy.

Although 459 (96%) of the 476 health visitor records were traced, the data collected were not always complete, especially for the controls and some infants had not reached the later assessment ages. Table 2 gives the number of infants with measurements available in each widow period, and as a percentage of the number of infants alive and old enough to have measurements taken when the form was completed. There were more weight than height measurements recorded. A high percentage of children had weight measurements recorded up to 10 months, although a slightly higher proportion of babies born to HIV positive mothers had measurements recorded within the window period due to close monitoring in the Edinburgh perinatal transmission study.[30] At 3 years, there are fewer recorded weights and the difference between babies of positive and negative mothers is more pronounced. There are fewer children with height measurements overall, and the differential of recorded height measurements by maternal HIV status is apparent from 6 weeks. A multiple logistic regression analysis of the pattern of missing data suggested that maternal HIV infection, a more deprived postcode sector of residence, a younger mother, being the firstborn, and having a birth weight less than the 10th centile were all significantly associated with having a recorded measurement. There was no evidence of an association with drug use.

The recorded weight measurements for the 213 females in the study are displayed in fig 1 with age and sex specific centiles. The boys' weight data show a similar pattern. The mean z scores for boys and girls combined, excluding infected infants, are given by visit in table 3. The cases are atypical, contributing to the inflated standard deviations of height and
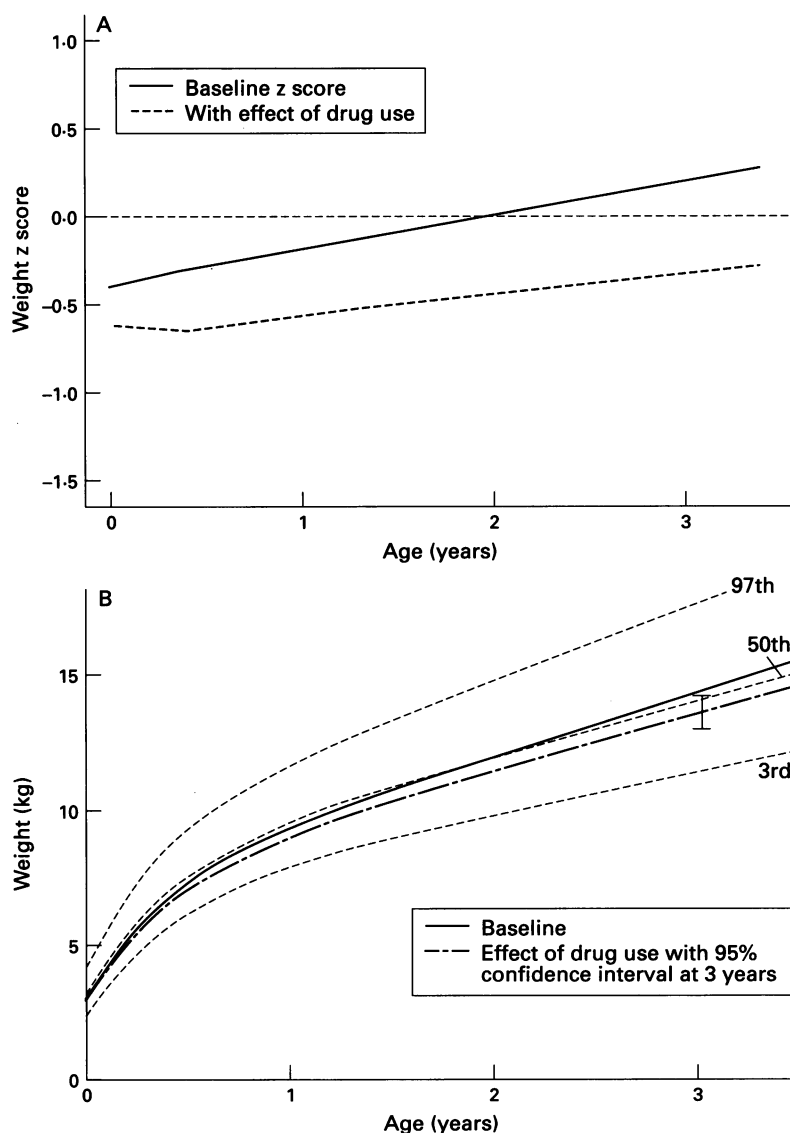

Figure 2   (A) Effect of maternal drug use on weight z scores. (B) Estimated weight for a baseline girl with and without the effect of maternal drug use against the UK 3rd, 50th, and 97th centiles. The baseline was a case singleton born to a mother who was neither infected nor used drugs during pregnancy and was of average height (160·6 cm) and age (23·6 years). The baseline mother smoked 10 or more cigarettes per day, lived in a postcode area with a deprivation score of 4, had no previous recorded pregnancies of 28 weeks or more, and bottle fed her baby.
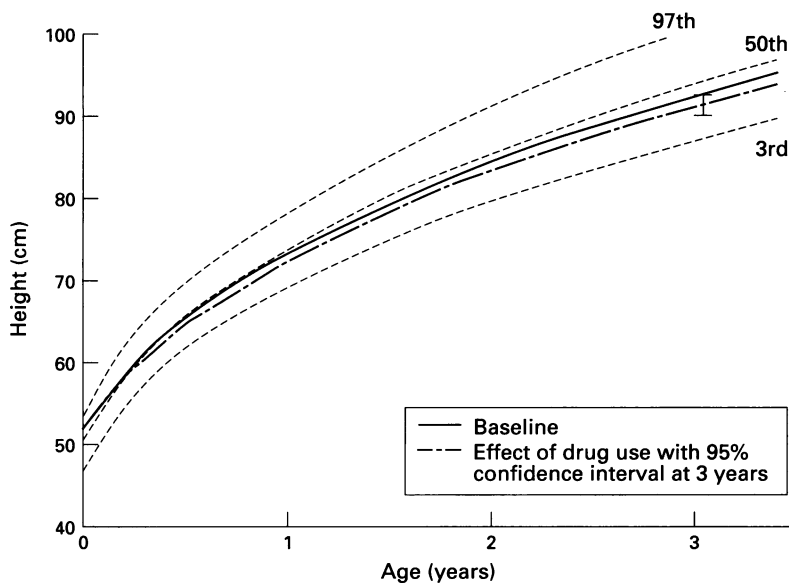
Figure 3   Estimated height for a baseline girl with and without the effect of maternal drug use against the UK 3rd, 50th, and 97th centiles. The baseline was a case singleton born to a mother who was neither infected nor used drugs during pregnancy and was of average height (160·6 cm) and age (23·6 years). The baseline mother smoked 10 or more cigarettes per day, lived in a postcode area with a deprivation score of 4, had no previous recorded pregnancies of 28 weeks or more, and bottle fed her baby.

weight z scores. The eight infected infants had a mean (SD) weight z score at birth of −0·73 (1·1) and the six survivors did not show catch up growth, with a mean of −1·1 (1·9) at 3 years. The adjusted estimates of the effect of maternal HIV infection on the intercept (size at 40 weeks), and growth (z score change per year) both up to, and from, 4 months are given in table 4. The estimated effect on size at 3 years from this model is also given. None of these estimates are significantly different from zero, although the pattern of estimates is consistent with a degree of accelerated growth in the first 4 months. There is no evidence that maternal HIV infection adversely affects size at 3 years and indeed the estimated effects are in the opposite direction. The differences between non-drug using uninfected cases and controls were negligible for all estimated coefficients, although the cases were consistently smaller, which suggests that contextual effects associated with being involved with a drug user's lifestyle are small.

Mothers who use drugs during pregnancy have babies who are lighter, but not shorter, at 40 weeks (table 5). These infants do not show the same degree of catch-up growth in weight during the first 4 months as those in the study whose mothers did not use drugs during pregnancy. There is some suggestion that their height growth also falters (p=0·051) in this period. Growth after this does not appear to be affected by drug use during pregnancy. The fitted z score growth slopes run roughly parallel after 4 months, resulting in babies born to the mothers using drugs during pregnancy remaining slightly shorter and lighter at 3 years of age. The fitted weight z score slopes with and without the effect of drug use in pregnancy are displayed in fig 2A, and the corresponding centiles for girls in fig 2B. Similarly, the fitted height centiles for girls are plotted in fig 3.

Discussion

There is no evidence to suggest that maternal HIV infection has adverse effects on growth in the first 3 years, indicating that the stresses of maternal HIV infection do not translate into decreased size of the infant. The finding that those babies born to women using drugs during pregnancy are slightly, but significantly, smaller at 3 years lends support to the argument for longer term effects of drug use in pregnancy[3-6] due to the numbers enrolled in this study. Growth in those exposed to drugs in utero was consistent with the pattern observed by Chasnoff and coworkers[11] with reduced fetal growth and retardation of growth continuing for a withdrawal period and then maintaining their centile position in relation to the children of women who did not use drugs in pregnancy. In comparison, children born to smokers also had slightly decreased size at 40 weeks but made up this deficit by 3 years, a pattern found elsewhere.[31] The estimated effect on weight z score at 3 years was −0·02 with 95% confidence interval −0·37 to 0·33.

Possible biases arise from the pattern of missing measurements. A high proportion (96%) of health visitor records were traced, but many did not include details of measurements within the window periods. It is plausible that healthy children who are obviously growing well do not warrant measurement at 3 years. In addition, there was evidence that maternal HIV status, although not drug use, improved the chances of a measurement being recorded due to the Edinburgh perinatal transmission study.[30] Taken together, these two observations suggest a possible bias in that children growing well in categories causing concern are more likely to be measured than children growing well who are not. This scenario would lead the study to underestimate the effect of the risk factors on growth. Thus drug use may have had a more severe effect than estimated here, and an association with maternal HIV infection may have been apparent. The most dramatic effects occur in the first 4 months, and the data in this period are reasonably complete; after this time estimated effects are slight. An analysis restricted to weight up to 10 months, for which at least 75% of measurements for each visit are recorded (table 2), similarly found no evidence of an adverse effect of maternal HIV infection. At 10 months the estimated effect on z scores was 1·04 (−0·22 to 2·3). Bias associated with covariates resulting from attrition at 3 years is minimised by the analyses, which are based on within-child growth patterns adjusting for covariate effects.

Exposure to opiates in utero may affect the mechanisms that control growth in humans. Naeye *et al* found that babies born to heroin addicted mothers were not only small for gestational age,[32] but also that individual organs were smaller and contained fewer cells than those of controls. An in utero growth disturbance is likely to continue until the drug has been expelled from tissue postnatally.

The lighter infants of drug using mothers may miss an important period for catch-up

growth in the first 4 months. Babies cross centiles in early infancy from their size at birth dominated by the mother's characteristics, to the channel for their genetic make-up.[28] There is wide variation in the growth slopes in this period, reflected by the wider confidence intervals for coefficients. Feeding patterns are established during this period. Babies born to drug using mothers are difficult to handle with excessive crying and a lack of bonding[11] and long acting opiates may inhibit feeding[33] thus their being at a disadvantage for growth during the early months.

Generally the data are reassuring. Maternal HIV infection does not adversely affect growth in the first 3 years, and the effect of drug use in pregnancy is limited to a small decrease in size at 3 years.

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