Limb-reduction defects and choriomic villus sampling

Sir,—Firth et al1 have described 5 infants with severe limb-reduction defects among 289 pregnancies in which chorionic villus sampling (CVS) at between 56 and 66 days of gestation had been done. 4 infants also had micrognathia and microglossia. The occurrence of this combination of defects after CVS is of serious concern to everybody doing prenatal diagnosis.

The exclusion of known syndromes1-3 cited by Firth et al as the context in which to judge these findings is based on our study.2 We found that 1 in 175 000 live births had the combination of limb-reduction defects with hypoglossia/micrognathia or hypoglossia-hypodactyly syndrome. However, this is a minimum estimate for this combination of defects because in registry data minor anomalies such as hypoglossia or micrognathia are underascertained. Registration of cases is in part from sources unsuited in picking up dysmorphic features or minor anomalies. However, it provides the only incidence figure in a context that is clear to our knowledge there are no other consecutive live-birth population studies on such defects.

In considering what categories of limb defect to compare with, other information needs to be taken into account. Instead of using only the very low incidence figure of a specific defect combination known to be underestimated it appears appropriate to use also the figure for particular defects of the hand and fingers. This is because these almost always come to the attention of the registry and thus present an upper limit of frequency of anomalies to compare with the observation in cases after CVS. The incidence figures for defects of various levels of the hand and fingers are summarised in the table.

In interpreting and comparing incidence figures, the classification system of limb-reduction defects used to derive the numbers must be kept in mind. We used the classification system based on the suggestions of the American Society of Surgeons of the Hand and of the International Society of Prosthetics and Orthotics4 and extended it to a hierarchy of categorising limb defects with respect to prenatal timing of development (unpublished). If incidences for limb reduction defects were calculated simply on the basis of the ICD-9 coding for bone defects, these figures would differ (table). The complete data and details of the classification system used will be published elsewhere.

Since CVS has been raised as the possible cause for very specific birth defects, we felt it useful to bring to attention these additional incidence figures from our study.


Twinning among HIV-infected mothers

Sir,—Three retrospective studies have revealed an unexpectedly high frequency of twins among HIV-infected children born in the USA.5-7 However, among six published prospective cohort studies only one, by our group in Brazil,4,5,7 has revealed a significantly greater number of twins among infants born to HIV-infected mothers compared with controls born to HIV seronegative mothers.4,5 Because all HIV-infected women do not transmit the virus to their children during pregnancy, one focus of research has been to identify the determinants of perinatal transmission. Transmission may be related to the mother's clinical or immunological status but discordance in HIV-infectious status in twins6 indicates that other factors, related to the fetus or to the circumstances of delivery, may also have a role.

Wisnia et al, in the Bronx (New York City), found a high frequency of twins among children born to seropositive mothers registered in foster-care programmes (7.9%, 6/80).8 Thomas et al made a similar observation in paediatric AIDS cases, also in New York (4.3%, 10/232).9 In Los Angeles, Frederick and Magnus, using a community-based active surveillance for paediatric HIV infection, also reported a high rate of twins.10 In all these studies, the comparison was with the frequency of twins reported in the general population of the study's catchment area. The main hypothesis proposed was that HIV-infected women may be more likely to have twin pregnancies than HIV-negative women because of a confounding factor such as drug use. Indeed, hormonal perturbations such as recent discontinuation of oral contraception have been hypothesised to induce twinning, and drug use might also be related to such hormonal changes.

Nevertheless, many biases could account for the above findings. For example, twin pregnancies might receive more care than singleton pregnancies and thus have a higher probability of being screened for HIV. Similarly, twins are often born premature or small for age; as a result they stay longer in the hospital and HIV infection is more likely to be tested for or diagnosed than it is in non-twins. Furthermore, if the probability of being infected relies on the probability of being infected (with symptoms or not), and on the assumption of an independent probability of perinatal infection for each twin, the probability of HIV infection within a twin pair (at least one twin infected) is greater than the probability of infection for a non-twin. With a rate of transmission of 30%, the probability would be 51% (1-0.35) for twins instead of 30% among non-twins. Finally, the risk of transmission of HIV from mother to infant might be increased in twin pregnancies since twins are more likely to be born premature and prematurity is related to HIV infection.

Only prospective cohort studies of infants perinatally exposed to HIV can give an accurate estimate of the rate of twinning in HIV-infected mothers and of the frequency of transmission of HIV to twins:

<table>
<thead>
<tr>
<th>Study</th>
<th>HIV+ mothers</th>
<th>HIV− mothers</th>
</tr>
</thead>
<tbody>
<tr>
<td>French cohort</td>
<td>3/313</td>
<td></td>
</tr>
<tr>
<td>European collab</td>
<td>3/264</td>
<td></td>
</tr>
<tr>
<td>Kretz et al.</td>
<td>10/10</td>
<td></td>
</tr>
<tr>
<td>Brazilian</td>
<td>4/0</td>
<td></td>
</tr>
<tr>
<td>Kenya</td>
<td>3/177</td>
<td></td>
</tr>
<tr>
<td>Kigali</td>
<td>3/215</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>251/1000</td>
<td>211/1288</td>
</tr>
</tbody>
</table>

The frequency of twinning in two European studies was low (1.5%). The twinning rate in HIV-infected mothers estimated from the African studies was higher (21.2%), not surprisingly since the frequency of twins is higher in Africa than it is in Europe or the USA. The African studies provide control groups of seronegative women matched for age and/or parity. In the control group, the twinning rate was 1.0%. Only in Brazzaville was there a significant difference (4/64 vs. 1/130) and in this case, the matching was done before delivery. These prospective studies do not specify the infectious status of the twins. In fact the transmission rate among twins may be more difficult to assess than among non-twins because twins are at a higher rate of dying very early, before HIV infection can be diagnosed definitely. This was so in our study in Brazzaville where, among 8 twins, 1 was stillborn, 4 died before one year, and among the 3 survivors 1 was infected and 2 were not.

To elucidate the causes of the high frequency of reported twins in the surveillance data, a higher perinatal transmission rate of HIV for twins may also be an additional cause of this apparent higher frequency in retrospective studies. Further prospective data are needed to resolve the issue of possibly increased twinning rates in HIV-infected mothers and potential mechanisms for it such as the possibility of a higher transmission rate in twins than in non-twins.

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Weekend migraine in men

SR= "Weekend headache" is well known to patients and physicians, and our experience is that a predominantly weekend incidence of migraine attacks is more common in men than in women. To test this we collected data by questionnaire from 151 consecutive patients with migraine1 (without aura 75, with aura 26) or tension-type headache2 (episodic 22, chronic 28). Mean age for these patients was 41 years range (range 17-64) and 23% were males.

The questionnaire inquired specifically whether a patient experienced symptoms predominantly on working days or at the weekend (or days off).

33 patients (21.9%) claimed to have weekend attacks. Their mean age was 37 years, close to that of the whole group of patients. However, the rate in males was 32% whereas in females it was only 19%. All 11 male weekend attack subjects were migraine patients (3 with aura, 8 without) but of the 22 women only 17 had migraine (3 with aura, 11 without) while 5 had tension-type headache. Weekend attacks do seem, therefore, to be more frequent in male migraine patients. In another study finding no significant increase in the frequency of migraine attacks at weekends, breaths were excluded.

The explanation offered for weekend headache is either the change in stress level or the sudden disappearance during the weekend of stress assumed to be more frequent in men, but women at weekends tend more than men do. Neurotic factors or other psychogenic explanations have been proposed, but change in sleep patterns has also been noted, the patient sleeping too long or for longer than usual at the weekend. Weekend delays in wake-up time and to-sleep time are more pronounced in men, who tend to have a shorter weekend awake-time. Other possibilities are missing breakfast (fasting) because of sleeping, dieing withdrawal, and an increased consumption of alcohol at the beginning of the weekend.

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Genotype and secretory response in cystic fibrosis

SR=—70% or so of mutations in cystic fibrosis (CF) are ΔF508 (loss of phenylalanine at position 508 in the CF transmembrane conductance regulator). Haplotyp data indicate that DNA markers closely linked to the gene locus suggest that the remainder of the CF gene pool consists of many different mutations,1 and more than seventy such mutations have been identified. Haplotype data suggest that pancreatic sufficient (CF-PS) and pancreatic insufficient (CF-PI) patients have different mutant alleles.2 It has been estimated that 8% of non-ΔF508 alleles may confer reduced pancreatic secretion.3 Similar haplotype associations with specific mutations have been shown in 320320.4,5,6

Attempts to correlate CF genotype with phenotype have produced inconsistent results. Keren et al7 suggested that the ΔF508 in homozygotes present earlier and show more frequent and more severe pancreatic insufficiency. The European working group on CF genetics has reported an increased incidence of meconium ileus in ΔF508 homozygotes.5 PS heterozygotes have been shown to have milder disease and to be diagnosed later.6 Johnson et al7 reporting on the phenotypic expression of ΔF508 in 235 CF patients attending the Copenhagen clinic, confirmed that homozygotes were diagnosed earlier, but they found no significant differences in respect of the proportions of meconium ileus at birth, liver involvement, or chronic Pseudomonas aeruginosa infection. We are unaware of any attempt to correlate genotype with objective measurement of residual secretory activity. We have reported that the underlying secretory defect in CF is expressed in the bowel and that the basal (unstimulated) potential difference (PD) was significantly reduced in CF patients, suggesting absence of