Letters to the Editor

Dizygous twinning and premature menopause in fragile X syndrome

SIR—The fragile X syndrome is caused by failure to produce the protein FMR-P. This failure is due to methylation precipitated by amplification of the CCG triplet repeat. The normal number of CCG repeats is 7–50. Individuals with 60–200 are unaffected carriers. Repeat numbers over 200 are associated with intellectual handicap in the male and may affect females to a lesser degree. Amplification of the CCG repeat number from one generation to another is thought to result from slippage. A normal repeat number is stabilised by approximately every 10th CCG repeat being replaced by an AGG. An uninterrupted stretch of CCG repeats over 30 may amplify between female generations.

Obligate carriers have an increased rate of dizygous twinning.[1] We have examined our pedigree data in which there is an individual with fragile X syndrome. All women with children and who have had their band size determined were included independently of whether any of their children were clinically affected with the fragile X syndrome. The probands were ascertained through a screening programme in the intellectually handicapped, not by the presence of twins. Repeat numbers were an estimate determined from band size by use of Southern blot analysis.

Two striking features (see table) are the increased twinning frequency in women of intermediate band size, and a return to the population rate in those with large expansions (0·6 kb). However, although the difference in the rates of medium expansion (0·1–0·59 kb) and mothers with no expansion (0 kb) is highly significant, whether calculated for mothers (p=0·001, 1 tail), or children (p=0·004, 1 tail), the contrast of medium with high expansion size is not quite significant for either mothers (p=0·093, 2 tail, given the lack of prior hypothesis) or children (p=0·156, 2 tail). Pooling the two expansion categories, there is still a significant contrast with the no expansion group (p=0·003, 1 tail) and children (p=0·009, 1 tail). This suggests that dizygous twinning is not a function of the failure of production of FMR-P protein. Variations in CCG repeat number have been considered to be normal polymorphisms but these results suggest that repeats may have a function that varies with number. That function may include a hypothalamic effect resulting in multiple ovulation.

	CCG repeat number		
	7–50 (0 kb)	50–200 (0·1-0·59 kb)	>200 (0·6 kb)
Number of women with children	173	253	55
Birthrate	2·4	2·9	2·5
Twins	3 (same sex)	23* (10 same, 13 different)	1† (same)
Birthrate of twins	1:140	1:34	1:139
Twinning rate of mothers	1:58	1:11	1:55

*2 pairs both affected; 5 pairs one affected; 7 carriers; 12 normal band size; 18 band size not determined but clinically unaffected.
†Not affected.

Table: **CCG repeats and birth results**

The menopause is initiated by a reduction in the number of follicles to below a thousand rather than chronological age.[2] It follows that the menopause might be earlier in multiple ovulators—it is earlier in mothers of twins. Martin et al[3] showed that multiple ovulation detected by ultrasound was more frequent in mothers of dizygous twins than in controls. Schwartz and colleagues[4] reported that early menopause is common in carriers of the fragile X syndrome, and this was confined to those with CCG repeats below 200. Rousseau et al[5] examined blood specimens from 10 624 females and found that 1 in 354 had CCG repeats in the carrier range. Most women with increased repeat numbers may not be at increased risk of having a child with the fragile X syndrome—ie, the CCG repeats may be adequately interspersed with AGGs and be stable. However, it may be that an above average number of CCG repeats is one of the causes of multiple ovulation and that these women may be at increased risk of having both dizygous twinning and early menopause. Conversely, among women who have early menopause and/or dizygous twins there will be those who have an increased number of CCG repeats and could be at risk of having a child with the fragile X syndrome.

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4 Schwartz C, Dean J, Howard Peebles P, et al. Obstetric and gynaecological complications in fragile X carriers. *Am J Med Genet* 1994; **51**: 400–02.
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Sumatriptan-induced chest pain

SIR—Houghton and colleagues (Oct 8, p 985) report oesophageal motility changes after a supratherapeutic dose of sumatriptan, and offer this finding as an explanation for sumatriptan-induced chest pain. We believe that these results should be regarded with caution.

First, of the five patients who had chest tightness, one did not display either abnormal amplitude or duration of contraction. The remaining four showed changes in duration of contraction only, with no abnormality of amplitude. Second, these changes were seen with doses almost three times higher than the standard 6 mg therapeutic dose. For Houghton and colleagues' explanation to hold, demonstration of similar motility changes in response to a clinically relevant dose is needed. Haemodynamic changes have been shown with the standard therapeutic dose of