Complications of pregnancy and benign familial joint hyperlaxity

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SUMMARY A family is described in which four generations were affected by benign familial joint hyperlaxity and, in the two generations for which obstetric data were available, pregnancies were complicated by unexplained mid-trimester vaginal bleeding. This prompted a study to determine whether unexplained antepartum haemorrhage (APH) and premature rupture of the membranes (PROM) both of which might reflect the structure of fetal collagen, were associated with joint hyperlaxity in offspring. The joint hyperlaxity of children born from such pregnancies was slightly greater than that found in age matched children born from uncomplicated pregnancies.

Key words: hypermobility (joint), labour (premature), abortion (threatened), abruptio placentae.

Early case histories suggested that the Ehlers-Danlos syndrome (EDS) was associated with obstetric abnormalities.^{1,2} More comprehensive surveys showed a clear link between premature labour, PROM, and EDS in the fetus.³⁻⁵ In 1969 Beighton showed that the variant of EDS usually associated with PROM was type I.⁶ This is one of the variants of this syndrome in which a clear abnormality of collagen has been identified.⁷

Some variants of the EDS are characterised by extreme vascular abnormality, particularly aneurysm formation. Other variants, such as type III, are characterised by minimal vascular change but pronounced peripheral joint hyperlaxity. The distinction between type III EDS and benign familial joint hyperlaxity is somewhat blurred. Joint hyperlaxity is associated with collagen laxity at other sites, and an increased incidence of mitral valve prolapse⁸ and of uterine prolapse⁹ have been described in association with benign joint hyperlaxity.

The bruising seen in patients with EDS is felt to be related to vessel wall fragility. There are isolated reports of pregnancies where the mother, and possibly the fetus, had EDS^{4,10} or benign hypermobility,¹¹ in which pregnancy was complicated by APH. The placenta is made up of fetal blood in

vessels composed of fetal connective tissue and also contains maternal blood in the intervillous spaces. The possibility that APH may be associated with joint hyperlaxity in the offspring was suggested to us by the following case history which prompted a more comprehensive study of the association between APH and PROM and familial joint hyperlaxity.

Patients and methods

INDEX CASE HISTORY

The index case, a 30 year old woman, presented in her sixth pregnancy with recurrent painless vaginal bleeding at 10, 19, and 21 weeks necessitating prolonged hospital admission. The placenta was situated in the upper uterine segment and there was no local cervical lesion. Her second pregnancy had ended in spontaneous abortion at eight weeks and her other four pregnancies had all been complicated by mid-trimester bleeding as shown in Fig. 1. She was hypermobile and when the Beighton variant¹¹ of the Carter and Wilkinson scoring system¹³ was applied she had a score of 7/9. Although her two brothers were unable to attend for assessment of joint laxity, one aged 40 had a history of recurrent dislocation of the patella and the other aged 36 wrote to report that he was 'double jointed'. Her three eldest children had peripheral joint laxity with scores of 3/9, 7/9, and 6/9. The mother of the index case was also hypermobile and when reviewed in

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clinic had a score of 7/9 at the age of 62. She had experienced bleeding in all her three pregnancies. Although the grandmother was dead, she was reported to have been 'very mobile', though no details of her obstetric history were available. None of the family members examined had any other stigmata of connective tissue disease such as cutaneous hyperlaxity or marfanoid habitus.

SURVEY OF OTHER FAMILIES

To determine whether this family was an isolated example, or whether this represented a more general association between benign familial joint hyperlaxity and APH or PROM, we performed a more systematic survey. Pregnancies recorded during the previous 15 years in the Yorkshire area

which had been complicated by unexplained APH or PROM were identified from the obstetric records of hospitals in Yorkshire. Unexplained APH was defined as significant bleeding occurring after the 28th week of pregnancy for which no cause was found. Patients with placenta previa and obvious placental abruption were excluded, but those with possible marginal abruption were included. PROM was defined as rupture of the membranes occurring before the onset of regular contractions and before 35 completed weeks' gestation. Mothers in whom APH or PROM was identified were asked by letter if they would be willing to bring the child resulting from the complicated pregnancy to a rheumatology clinic for assessment of joint laxity. The joint laxity of the child was then measured by the Beighton

MALE

FEMALE

NO BLEEDING IN PREGNANCY

BLEEDING AT WEEKS GESTATION MARKED IN ()

OBSTETRIC DETAILS NOT KNOWN

[] CARTER WILKINSON SCORE OR HYPERMOBILITY HISTORY

NT = NOT TESTED

AGE

AGE TESTED

Fig. 1 Family tree demonstrating association between mid-trimester bleeding in pregnancy and familial hyperlaxity.

modification¹² of the Carter and Wilkinson scoring system.¹³

A control group approximately matched for age was recruited from local schools. These individuals were assessed for peripheral joint laxity by the same method, it being assumed that these subjects were born from uncomplicated pregnancies. This assumption was felt to be justified as the accepted prevalence in a normal population varies from 1 in 100 to 1 in 500 for unexplained APH and 1 in 50 to 1 in 300 for PROM before the onset of premature labour.

Results

As a result of our survey 14 children were identified who had been born from complicated pregnancies, were still living in the Yorkshire area, and whose mothers were agreeable to their attending clinic. Table 1 shows the joint laxity scores for the nine

Table 1 Joint laxity scores for children resulting from pregnancies complicated by premature rupture of the membranes

Age	Sex	Carter Wilkinson score
12	F	2/9
9	M	2/9
13	F	0/9
10	M	4/9
9	M	0/9
13	M	0/9
10	M	4/9
14	M	0/9
10	F	4/9

Table 2 Joint laxity scores for children resulting from pregnancies complicated by antepartum haemorrhage

Age	Sex	Carter Wilkinson score
11	M	0/9
16	F	2/9
13	M	4/9
14	F	5/9
9	F	2/9

Table 3 Comparison of joint laxity in PROM and APH populations with the joint laxity in age and sex matched controls

	Age (mean) (years)	Percentage with score of 4/9 or more	Percentage with score of 3/9 or 2/9	Percentage with score of 1/9 or 0/9
PROM (n=9; M6:F3)	11.1	33.3	22.2	44.4
Control (n=24; M11:F13)	10.8	20.8	33.3	45.8
APH (n=5; M2:F3)	12.6	40.0	40.0	20.0
Control (n=34; M17:F17)	13.0	26.5	47.0	26.5

children resulting from pregnancies complicated by PROM and Table 2 the joint laxity scores for the five children resulting from pregnancies complicated by APH. The Carter Wilkinson score was 4/9 or more for 3/9 children resulting from pregnancies complicated by PROM and for 2/5 children resulting from pregnancies complicated by APH. Table 2 compares the distribution of joint laxity in these two populations with approximate age matched control groups of similar sex distribution. For both PROM and APH there is a tendency for the resulting children to have a more pronounced degree of joint laxity than the age matched control subjects. None of the case or control children had any other stigmata of connective tissue disease.

Discussion

The family history shows a previously undescribed association between benign familial hyperlaxity and recurrent unexplained mid-trimester bleeding in pregnancy. Because of the pronounced hyperlaxity throughout the family it is not clear whether the mid-trimester bleeding reflects the maternal hyperlaxity or the fetal hyperlaxity. The format in which obstetric records are kept in Yorkshire does not easily allow the tracing of children resulting from other pregnancies that have been complicated by mid-trimester bleeding. Our more systematic survey concentrated on other possible complications of pregnancy that may reflect abnormal collagen structure. A major difficulty was the relatively small number of children we were able to trace resulting from pregnancies complicated by PROM and unexplained APH. This reflects the relative rarity of these two conditions. Nevertheless, this rarity allows us to have a considerable degree of confidence that subjects selected for the control group (for whom it was impossible to trace the obstetric records) were not born from pregnancies associated with these complications. The assessment of joint hyperlaxity in children is not easy, and it is possible that if the children had been examined at a greater age, their laxity would have been even more pronounced than that of the normal population. Nevertheless, the

comparison with age matched controls still suggests the tendency for hyperlaxity to be more pronounced in the offspring of pregnancies complicated by PROM and APH.

Collagen structure is unlikely to be the only single factor in the pathogenesis of PROM and APH. On this basis we would not anticipate a strikingly high correlation between the abnormal pregnancies and this single pathogenetic factor. Indeed, not all have shown a convincing association between PROM and fetal membrane strength,¹⁴⁻¹⁶ though methods for measuring this vary. Some have shown a firmer adherence between amnion and chorion in prematurely ruptured membranes and suggested a possible mechanism for this association.¹⁷ Others have shown reduced elasticity in prematurely ruptured membranes.¹⁸ Other factors will have influence on the pressure to which membranes are subjected and local infection is conventionally held to be among the most common of the environmental factors that may contribute.

Against this background, a study on the relatively small number of subjects available to us is unlikely to be conclusive, though we feel our results provide some support for an association between familial benign joint hyperlaxity in the child and PROM and APH. They also suggest that the association between hyperlaxity and mid-trimester bleeding would be worthy of further study.

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