Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study compared a strategy of prenatal population-based screening with no screening (usual care) for carriers of the fragile X mental retardation protein 1 (FMR1) premutation in all pregnant women.

Type of intervention
Screening.

Economic study type
Cost-utility analysis.

Study population
The hypothetical population comprised pregnant women.

Setting
The setting was the community. The economic study was carried out in California, USA.

Dates to which data relate
The studies providing the effectiveness evidence were from 1993 to 2004. For cost data, the date range was 1994 to 2002. The price year was 2004.

Source of effectiveness data
The evidence was derived from a review or synthesis of completed studies and estimates based on authors’ assumptions.

Modelling
A decision analytic model was developed to compare a policy of widespread prenatal screening for fragile X carriers with no screening. The model was based on a decision tree.

Outcomes assessed in the review
The outcomes in the baseline model included:

- the number of pregnancies available for screening,
- full FMR1 mutation prevalence,
- the premutation expansion rate,
- the sensitivity and specificity of the genetic test,
the rate of women with a positive carrier test that would undergo amniocentesis, and
the rate of women with fragile X who would undergo pregnancy termination.

Study designs and other criteria for inclusion in the review
The authors reported that the English literature was searched for the terms "fragile X", "FMR1", "permutation" and "triple repeat expansion". No other inclusion or exclusion criteria were reported.

Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
Not reported.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
Twenty-nine primary studies were included in the review as sources of effectiveness evidence.

Methods of combining primary studies
A narrative method was used. To estimate the carrier prevalence, the authors weighted the different rates according to sample size. Carrier prevalence and the prevalence of fragile X in the population were used to estimate the rate of premutation expansion.

Investigation of differences between primary studies
Not reported.

Results of the review
The baseline model considered 4 million pregnancies annually, of which 87% would be available for screening.

The full FMR1 mutation prevalence was assumed to be 1 in 4,000.

A sensitivity of 99% and a specificity of 99.9% were used for the genetic test.

A rate of 92% was used for women with a positive carrier test that would undergo amniocentesis, and a rate of 87% for women with fragile X that would undergo pregnancy termination.

The carrier prevalence was estimated to be 0.003305, or approximately 3.3 per 1,000. A value of 16.3% was used for the expansion rate.

Methods used to derive estimates of effectiveness
The authors also made assumptions in the analysis.

Estimates of effectiveness and key assumptions
The authors assumed a 1 in 4,000 rate of fragile X among men, a 1 in 8,000 rate of fragile X among women, and a 1 in 8,000 rate of full mutation carriers among women. Given these prevalence rates and the prevalence rate of premutation carriers of 3.3 per 1000, an expansion rate of 11.3% was estimated. The risk of procedure-related loss secondary to amniocentesis was estimated to be 0.005.

It was assumed that 80% of women could be screened with polymerase chain reaction (PCR) alone, whereas the remaining 20% would require Southern blot analysis.

Measure of benefits used in the economic analysis
The authors used the number of fragile X diagnoses and quality-adjusted life-years (QALYs) as measures of benefit. The utilities were taken from the literature on patients’ preferences toward Down syndrome because they provided a reasonable upper estimate of what would be expected for preferences toward a foetus with fragile X syndrome. The utilities used were measured by the standard gamble method. They were 0.93 for a procedure-related loss, 0.92 for undergoing a second-trimester termination of pregnancy, 0.81 for having a child with fragile X syndrome, and 0.96 for having a false-positive screen. The health benefits were discounted at a rate of 3%.

Direct costs
The direct costs included the DNA analysis costs for a PCR-based fragile X screening test and for a Southern blot test. These screening costs comprised both the physicians and patients’ time costs, administration of screening, clinic and laboratory overheads. The time costs for the physician covered counselling and discussion of the results. The time costs for the patients covered counselling time, marginal time obtaining the specimen, and time to read fliers. Also included were a consultation with a genetic counsellor, amniocentesis costs, the cost of pregnancy termination and the cost of spontaneous second-trimester loss. The lifetime cost of raising and caring for an individual with fragile X syndrome was also included. All the costs were discounted at a rate of 3%. The cost estimates were taken from the existing literature. All historical costs were inflated to year 2004 dollars using the Consumer Price Index.

Statistical analysis of costs
The costs were treated deterministically. No statistical analysis of the costs was reported.

Indirect Costs
Although the authors stated that a societal perspective was considered, the indirect costs associated with productivity loss were not reported.

Currency
US dollars ($).

Sensitivity analysis
A univariate sensitivity analysis was performed in which different inputs of the model were varied. The prevalence of the premutation, the rate of expansion, the rate of women proceeding with amniocentesis, the acceptance of a termination of pregnancy, and the number of pregnancies per woman were varied over feasible estimates. A two-way sensitivity analysis was also carried out in which the prevalence of the carrier population and the expansion rate were varied simultaneously. When the ranges of outputs crossed above or below the different thresholds of cost-effectiveness, a threshold analysis was performed (using $100,000/QALY as the threshold value).

Estimated benefits used in the economic analysis
The screening strategy would lead to the identification of 80% of the approximately 750 fragile X-affected foetuses annually.
Ninety-eight diagnoses would be missed because of the 13% of patients who presented too late to obtain prenatal diagnosis. Another 52 would be missed because of patients declining amniocentesis and 8.95 fragile X foetuses would be identified for each procedure-related loss caused by amniocentesis.

In addition, to detect 1 foetus with a full fragile X mutation, nearly 24 women would need to undergo amniocentesis.

The number of QALYs was not reported.

**Cost results**
The total cost of each strategy was not reported in the text.

**Synthesis of costs and benefits**
The costs and benefits were summarised in the form of a cost-effectiveness ratio and a cost-utility ratio, by dividing the total costs by the number of fragile X diagnoses or QALYs saved.

The costs of screening and testing would be $581,295 per fragile X diagnosis.

The screening programme yielded a cost-utility ratio of $14,858 per QALY.

Throughout the entire reasonable range of carrier prevalence and expansion rate, the screening programme remained cost-effective, ranging from $7,748 to $21,613 per QALY. With 2 and 3 children, and throughout the range of the utilities, the screening programme remained cost-effective. The only cost that the screening programme was particularly sensitive to was the cost of the screening test. The threshold analyses found that when the screening costs reached $150, or when 55.8% of women with fragile X premutation underwent amniocentesis, the programme would reach the threshold of cost-effectiveness of $100,000 per QALY.

**Authors’ conclusions**
A prenatal fragile X carrier screening programme that aimed to screen all pregnant women, regardless of family history or specific risk factors, would be cost-effective throughout a reasonably wide range of assumptions, and applying a commonly used cost-effectiveness threshold ($100,000 per quality-adjusted life-year, QALY).

**CRD COMMENTARY - Selection of comparators**
No explicit justification was provided for the comparator used. The authors noted that carrier screening is recommended only for those patients with a specific family history. By using a no-screening strategy as the comparator, the active value of the screening could be evaluated. You should decide if the comparator represents current practice in your own setting or whether other comparators, such as screening for those patients with a specific family history, could also be relevant.

**Validity of estimate of measure of effectiveness**
Although the authors stated that they conducted a systematic review of the literature, they did not provide details of the methodology for selecting and reviewing the literature. The authors used data from the primary studies selectively. They did not consider the impact of differences between the studies identified when estimating effectiveness. The estimates were investigated using sensitivity analyses, and the authors justified the ranges selected on the basis of the literature. Authors’ assumptions were also used to derive parameters; these values were also justified on the basis of the literature, but they were not tested in a sensitivity analysis.

**Validity of estimate of measure of benefit**
The authors used QALYs as the measure of benefits. The estimation of utility weights was taken from the literature. Preferences were derived from a different syndrome which might have had an impact on the results, although the
authors stated that the different syndromes share phenotype features and thus make the comparison of women's preferences reasonable.

**Validity of estimate of costs**

Although the authors reported that the study was carried out from a societal perspective, no indirect costs were included. Their influence on the results could be significant, especially as the proportion of working women in this age group is probably large. The costs and the quantities were not reported separately, which would make it difficult to rework the analysis for other settings. Sensitivity analyses of the screening test costs were conducted, and the model proved to be particularly sensitive to these costs. Discounting was appropriately carried out since the time horizon of the model was longer than 2 years. A revaluation of the costs was carried out and the price year was reported, which will aid any future reflation exercises.

**Other issues**

The authors compared their findings with those from other studies and generally found them to be concordant. The issue of the generalisability of the results to other settings was not addressed. The authors' conclusions reflected the scope of the analysis. The authors acknowledged several limitations to their study, which were mainly those related to any model-driven analysis. Specifically, the authors acknowledged that they used preferences derived from a different syndrome and this might have had an impact on the results. There were also several other factors that they did not include in the model, such as the costs saved from overlapping screening programmes for other genetic disorders, and the long-term screening benefits into the next generation when many fewer women would need to be screened because of information from their mothers' screens. Also, the benefits to the rest of the family members of prenatal diagnosis of a fragile X foetus, additional health benefits that might be realised to the patient being screened, and the potential psychosocial aspects of screening.

**Implications of the study**

The results of this study support population-based prenatal carrier screening for fragile X syndrome. The authors suggested that at present there might be significant logistic and manpower obstacles to initiating such a programme. However, such counselling and screening could easily be added to that used for cystic fibrosis and Down syndrome, so that not even an additional blood draw would be required. They also suggested that before the widespread adoption of such a programme, prospective studies of fragile X screening programmes should be performed to better understand patients' attitudes, preferences and behaviours. The determination of actual preferences for fragile X carrier screening from women considering prenatal testing and their psychological outcomes, through prospective studies, may ultimately impact upon this analysis.

**Source of funding**

Supported by the National Institute of Child Health and Human Development (grant HD01262) and the California Pacific Medical Research Institute.

**Bibliographic details**


**PubMedID**

15970847

**DOI**

10.1016/j.ajog.2005.02.052

**Indexing Status**

Subject indexing assigned by NLM