Fragile X syndrome (FXS) is an inherited disorder that causes learning difficulty. The disorder affects an estimated one in 4000 males and one in 8000 females. Affected males are generally unable to live independently, while affected females have learning difficulty but may live independently. There is no cure for FXS. Management of affected individuals is through specific educational and psychosocial interventions and treatment of any clinical symptoms.

There are about 10,000 FXS patients in England and Wales. Since the annual cost to the NHS for managing a moderately affected adult was approximately 20,000 GBP (1995 data), the total annual cost of managing FXS patients can be estimated to be 200 million GBP in England and Wales.

FXS is caused by a mutation of the FMR1 gene, which is located in the Xq27.3 region of the long arm of the X chromosome. It contains a variable trinucleotide repeat [cytosineguanineguanine (CGG)] which can become unstable over successive generations. The number of CGG repeats within a gene will determine whether the individual has a normal allele (<55 repeats), premutation (55200 repeats) or a full mutation (>200 repeats). All males with full mutation (FM) and about half of females with FM are affected with learning difficulty. People with premutation (PM) are not affected in general. The PM can become unstable on maternal transmission and mothers with PM may have affected children. The risk of expansion from PM to FM depends on the number of CGG repeats in the maternal allele and other factors. The expansion risk from PM to FM is much greater in affected families than in the general population.

Options for population and targeted screening for FXS and carriers have been the focus of two previously published HTA reviews. However, the two previous HTA reports reached contrasting conclusions and recommendations for further research. The different approaches recommended by the two HTA reviews were prenatal screening of all apparently low-risk women, and cascade testing of high-risk women following systematic case finding. This review aims to bring together the findings of the two previous HTA reports.

Authors’ conclusions

The empirical evidence suggested that both prenatal screening and cascade screening are feasible and acceptable. Both prenatal screening and active cascade screening can reduce the number of births of FXS children and are cost-saving in the long term. Population-based prenatal screening is more efficacious and has a greater impact on the population, but it will also cost more than active cascade screening. The active cascade screening of affected families is more efficient, cheaper, but less effective than a population-based prenatal screening.

Since both prenatal screening and active cascade screening have advantages and disadvantages, we believe that both strategies should be evaluated in large-scale trials. It may also be important to explore and evaluate whether and how the different strategies could be simultaneously or sequentially combined.

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