Screening for activated protein C resistance before oral contraceptive treatment: a pilot study


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
Laboratory screening for congenital thrombophilic alterations in women who wished to start oral contraceptive (OC) treatment. At the first screening, the following tests were carried out on blood taken from the subjects. (1) Activated protein C resistance (APCR), using the in-house clotting method proposed by de Ronde and Bertina. The inter-assay coefficient of variation (CV) was 6.1% for normal, and 5.2% for abnormal samples. The cutoff value for abnormal cases was set at less than 0.75 of a normalised ratio. (2) Protein C activity (PC), by means of a commercial chromogenic method using Protac activation. The inter-assay CV of the method was 3.7% for normal and 5.2% for abnormal samples. Values below 62% were considered to be abnormal. (3) Protein S activity (PS), by a commercial clotting method. The inter-assay CV was 3.9% for normal, and 5.4% for abnormal samples. Values below 62% were considered as abnormal. (4) Antithrombin III activity (ATIII), using a commercial chromogenic method. The inter-assay CV was 2.6% for normal and 4.1% for abnormal samples. Abnormal values were considered to be those below 75%. Women with abnormal or borderline results at first screening were advised to have a second blood sample, to repeat the altered test and perform the corresponding immunologic assay or DNA analysis for factor V Leiden mutation in cases with altered APCR. For all the tests, an internal quality control was routinely performed. External quality assessment was also carried out for antithrombin III, protein C activity and activated protein C resistance.

Type of intervention
Screening and diagnosis.

Economic study type
Cost-effectiveness analysis.

Study population
Women referred to the family planning clinic for a first ever OC treatment course and who, after gynecological examination, were found to be eligible for treatment. Patients were excluded if they were currently undergoing OC treatment, had had previous oral contraceptive treatment, and were over 45 years of age.

Setting
Hospital family planning clinic. The economic analysis was carried out in Italy.

Dates to which data relate
Effectiveness and resource use data corresponded to patients referred to the study clinic from September 1995 to May 1997. The estimate of the incidence of thromboembolic events per 10,000 person years for subjects with factor V Leiden and current OC users was based on a single study published in 1994. The price year was 1997.

Source of effectiveness data
The evidence for the final outcomes was based on a single study and an assumption made by the authors, which was...
also based on a single published study.

**Link between effectiveness and cost data**
Costing was performed on the same patient sample as that used in the effectiveness analysis. It is not entirely clear, however, whether the costing was carried out prospectively or retrospectively.

**Study sample**
Power calculations were not used to determine the sample size. The study sample consisted of 525 women with a mean age of 21.9 years (range: 14 - 44). 75% of the subjects were under 25 years of age. 38 subjects were excluded because they did not meet the study inclusion criteria.

**Study design**
This was a prospective cohort study, carried out in a single centre. The duration of the follow-up does not appear to have been reported. Regarding loss to follow-up, it was reported that three subjects refused to undergo second examinations. The results of blood tests, available in about 10 days, were sent to the gynecologist. Initiation of OC was discouraged in the presence of certain alterations. An immediate second blood sample was suggested to repeat the altered test and/or for further analysis.

**Analysis of effectiveness**
The principle used in the analysis of effectiveness appears to have been both intention to treat and treatment completers only. The clinical outcome measures were normal and abnormal results (APCR with and without V Leiden, PC, PS, and ATIII) after first and second screening.

**Effectiveness results**
At first screening, completely normal results were recorded in 485 (92.4%) of the study subjects. The remainder showed single alterations (n=34) or multiple alterations (n=6). At second examination, activated protein C resistance (APCR) was confirmed in 21 cases (4.0%, 18 with factor V Leiden), protein C reduction in 8 (1.5%), and protein S reduction in 2 (0.4%) cases. No cases with antithrombin III deficiency were detected. Overall, confirmed thrombophilic alterations were detected in 28 of the 525 subjects investigated (5.3%). This incidence might have been as high as 5.9% if the alterations found at first screening had been confirmed in the three subjects who could not be re-examined.

**Clinical conclusions**
Thrombophilic alterations were confirmed in 28 (5.3%) of the women investigated and excluded in 9 at re-examination. As expected, no case of antithrombin III deficiency was detected, because of the limited number of women investigated. Even using a specially determined lower cutoff value (set as 62%) for measuring protein C activity, a larger number of women than expected still had abnormal results; in none of these could it be clearly shown that the alteration was inherited. It may be inferred that, if this test were widely performed in such a population, an abnormally low protein C activity would be wrongly diagnosed in many cases. In the present study, three individuals consistently had an APCR alteration while not being FV Leiden carriers. Whether reduced response to activated protein C in the absence of FV mutation is associated with thrombotic risk is still debatable.

**Methods used to derive estimates of effectiveness**
Assumptions were made by the authors based on a single published study.

**Estimates of effectiveness and key assumptions**
The estimated incidence of thromboembolic events per 10,000 person years of subjects with factor V Leiden and current OC users was 28.5.
Measure of benefits used in the economic analysis
The number of confirmed altered cases detected was the initial benefit measure adopted in this study. The number of thromboembolic events was used as an extra measure of benefit, and was briefly addressed in the discussion section of the paper.

Direct costs
Costs were not discounted because of the short time frame of the cost analysis. No quantities besides the number of tests carried out were reported separately from the costs. Cost items were not reported separately. Cost analysis covered the estimated overall costs necessary to carry out all the first screening and confirmatory tests in the entire study sample, as well as the cost estimates for detecting a single thrombophilic alteration for each assay considered, using the unitary costs of each test. The unitary cost of each test included the costs of purchasing kits or reagents, external quality control, the specifically used instrumentation, the staff, and computers and all other general tools used in the laboratories. The perspective adopted in the cost analysis was not explicitly reported. The median values of the unitary cost for each test recorded among all the regional laboratories were used to estimate the laboratory cost of the tests. The price year was 1997. The cost analysis did not cover the cost of complementary investigations (genetic analysis for Factor V Leiden mutation, immunologic assay of protein C, protein S, or antithrombin III).

Indirect Costs
Indirect costs were not considered.

Currency
Italian lira (L). The exchange rate recorded on November 18, 1998 was reported to be US$1 = L1650.

Sensitivity analysis
No formal sensitivity analysis was performed. However, the distribution of protein C activity results obtained in the entire study sample by using two different cut-off levels (62% and 70%) was shown as a chart. Furthermore, the paper pointed out the effect of a very low cost used in the study hospital as opposed to the more expensive median cost of all the regional laboratories on APCR.

Estimated benefits used in the economic analysis
The number of confirmed alterations were as follows: APCR, 21 cases; PC, 8 cases; PS, 2 cases; and ATIII, 0 cases. The number of thromboembolic events per 10,000 person years of subjects with factor V Leiden and current OC users was 28.5.

Cost results
The total costs of examining all the 525 subjects were as follows: APCR, $9,097; PC, $10,988; PS, $15,591; and ATIII, $2,696.

Synthesis of costs and benefits
The global estimated cost of detecting one altered case was: $7,795 for PS, $2,696 for ATIII (no case found), $1,374 for PC and $433 for APCR. The cost necessary to prevent one thromboembolic event per year in subjects with activated protein C resistance has been estimated to be as high as $152,000, taking into account the estimate of an incidence of 28.5 thromboembolic events per 10,000 person years for subjects with factor V Leiden and current OC users, and a 4% prevalence of the alteration in the general population, as in the present study.

Authors' conclusions
The present study confirms that extensive thrombophilic screening before OC treatment is not currently advisable. APCR assessment, however, seems to have a favourable cost-effectiveness ratio. The alteration is frequent and has a synergistic effect with OC. The sensitivity and specificity of some methods are good. Family history is unreliable for singling out possible carriers. Finally, carriers can be fully informed of their increased thrombotic risk if treated with OC and can receive thromboprophylaxis during life situations associated with high thrombotic risk such as pregnancy.

CRD COMMENTARY - Selection of comparators
The strategy of not performing thrombophilic screening was implicitly regarded as the comparator. This allowed the active value of the intervention to be evaluated.

Validity of estimate of measure of effectiveness
The effectiveness results are likely to be internally valid given the prospective nature of the study design. However, the lack of power calculations raises doubts regarding the adequacy of the sample size to address the main study questions. Furthermore, no systematic literature review appears to have been performed to derive the value of the incidence of thromboembolic events. The study sample appears to have been representative of the study population.

Validity of estimate of measure of benefit
The estimate of measure of the main health benefit was directly based on the effectiveness results. The estimate of the incidence of thromboembolic events per 10,000 person-years of subjects with factor V Leiden and current OC users was based on a single published study. The choice of the estimates was justified. The effects of diagnosing APCR on the prevention of events resulting from inherited thrombophilic risk was not fully captured in the study.

Validity of estimate of costs
The validity of the cost results was enhanced by the following features of the cost analysis: adequate details of the methods of cost estimation were given and the price year and exchange rate year were specified. However, the following issues may limit the validity of the cost results: quantities were not reported separately from the costs; the perspective adopted in the cost analysis was not explicitly reported; it is not entirely clear whether the cost analysis was based on true costs or on charge data; the cost analysis does not appear to have been comprehensive as some components of total costs such as the costs of complementary investigations were omitted from the analysis; statistical analysis was not performed on either resource use or cost data; the effects of the screening tests on indirect costs (productivity loss) were not addressed. The cost results may, therefore, not be generalisable outside the study setting.

Other issues
Given the limitations of the study design and the lack of extensive sensitivity analysis and statistical analysis of costs, some degree of caution may need to be exercised in interpreting the study results. The issue of generalisability to other settings or countries was not addressed, although appropriate comparisons were made with other studies. The degree to which the study sample was representative of the study population was not addressed. An incremental cost-effectiveness ratio could have been calculated in the comparison of the different tests by using one of the tests as the comparator. It was noted that a large number of events in individuals with APCR can be prevented before age 50 years as a result of diagnosing the alteration, thus leading to a much more accessible cost per thrombotic event prevented.

Implications of the study
Extensive screening should be limited to cases with a personal or family history of venous thromboembolic events. The compiling of such a history is highly recommended before OC prescription.

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