Prospective epidemiologic study of the outcome and cost-effectiveness of antenatal screening to detect neonatal alloimmune thrombocytopenia due to anti-HPA-1a


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
Two antenatal screening strategies for the detection of neonatal alloimmune thrombocytopenia (NAIT) due to anti-HPA-1a were examined. The first strategy was to screen all pregnant women (excluding those with a previously affected pregnancy) and genotype partners where the mother is HPA-1a-negative. The second strategy consisted of screening all pregnant women (excluding those with a previously affected pregnancy) and genotype partners where the mother is HPA-1a-negative and develops alloantibodies. NAIT was defined as a confirmatory platelet (PLT) count below the lower limit of the normal range (<150 x10^9/L). Severe thrombocytopenia was defined using a higher threshold (<50 x10^9/L).

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised pregnant women.

Setting
The setting was secondary care. The economic study was carried out in the UK.

Dates to which data relate
The effectiveness and resource use data were gathered from August 1999 to March 2001. The costs were expressed using 2003/04 prices.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing was carried out prospectively on the same sample of women as that used in the effectiveness analysis.

Study sample
Power calculations were not reported, but a very large sample of pregnant women was used. All pregnant women (10 to 16 weeks) booking for blood grouping and antenatal red blood cell antibody screening at antenatal centres over the study period were contacted and asked to participate. Of the 26,506 women who were phenotyped, 546 were initially...
found to be HPA-1a negative. Of these women, 152 declined to participate or could not be contacted, while 394 agreed to participate. The number of women with confirmed HPA-1a-negative samples was 327. A group of 322 consecutive HPA-1a-positive controls was selected from among the 25,705 women who were HPA-1a positive.

**Study design**
This was a prospective, controlled cohort study that was carried out at seven antenatal screening centres in Scotland. The length of follow-up was 2 years. Confirmed HPA-1a-negative women were monitored for the development of HPA-1a alloantibodies at 22 to 24 weeks, 32 to 36 weeks, at delivery, and at 10 to 14 days after birth. Of the 327 women participating in the screening group, follow-up data were available for 318 women. Of the 322 women in the control group, 266 completed the follow-up assessment. Clinical data were obtained through direct patient interview and a review of medical case notes and clinical laboratory records.

**Analysis of effectiveness**
The analysis of the clinical study was restricted to the sample of women who completed the follow-up assessment. The outcome measures used in the study were:

- the prevalence of confirmed HPA-1a negativity;
- the incidence of newly identified HPA-1a alloantibodies in HPA-1a-negative women;
- the association of newly identified HPA-1a alloantibodies in HPA-1a-negative women with HLA-DB3*01+;
- the number of new cases of NAIT;
- the number of new cases of severe NAIT; and
- the number of cases of intracranial haemorrhage (ICH).

The baseline comparability of the study groups was not demonstrated.

**Effectiveness results**
The prevalence of confirmed HPA-1a negativity was 1.7%.

The incidence of newly identified HPA-1a alloantibodies in HPA-1a-negative women was 7.9%.

The earliest appearance of antibodies was 21 weeks in 2 women, while 3 women produced antibodies after 28 weeks. These data appear to suggest that NAIT is very unlikely to appear in a genuine first-time pregnancy.

There was a significant association of HLA-DRB3*01 (DR52a) with anti-HPA-1a alloimmunisation.

The data suggested that, among HPA-1a-negative women, the presence of HLA-DRB3*01+ positivity had a positive predictive value of 16.8% and a negative predictive value of 96% for the development of HPA-1a alloantibodies.

Eight (32%) of the 25 antibody-positive women with no history of NAIT (2.5% of the 318 HPA-1a-negative women) delivered thrombocytopenic babies. This suggested that there were 43 new cases of NAIT per 100,000 live births.

Three of the 8 babies experienced moderate NAIT, while five experienced severe NAIT. Thus, there were 27 new cases of severe NAIT per 100,000 live births.

Of the 5 babies diagnosed with severe NAIT, one had spontaneous resolution with the PLT count gradually increasing to normal levels by day 4. The other 4 severely thrombocytopenic infants received prompt transfusions of 1 or 2 units of HPA-1b1b PLTs derived from blood donors by apheresis.
Three babies demonstrated signs of minor haemorrhage but none experienced serious clinical sequelae.

The number of ICHs per 100,000 live births was 0.

The proportion of delivered babies with mild to moderate thrombocytopenia (81 - 142 x10^9/L) in the control group was 2.6%, but all of these babies recovered spontaneously without adverse clinical sequelae.

Clinical conclusions
The effectiveness analysis showed that antenatal screening was more effective in detecting NAIT cases than no screening.

Modelling
A model based on a decision tree was constructed to assess the costs and benefits of the antenatal screening strategies in comparison with no screening for a cohort of pregnant women. Women who entered the model could receive one of the two screening options or no screening. In the case of receiving a screening option, a phenotyping test indicated whether the mother was HPA-1a-positive or -negative. HPA-1a-negative women were tested for HPA-1a alloantibodies and a subsequent decision was made regarding genotyping the partner. If the partner was genotyped as HPA-a1a homozygous or HPA-1a1b heterozygous, the mother was monitored and arrangements were made to ensure that HPA-1a-negative PLTs were available at delivery, in case transfusions were required. Infants were born either alive or dead. Of those alive, thrombocytopenia (possibly NAIT) was suspected in some infants, whereas it was not suspected in others. A confirmatory cord PLT count provided information on whether the PLT count was within the normal range or not, and distinguished neonates with mild and/or moderate NAIT from those with severe NAIT. The structure of the tree was represented graphically.

Measure of benefits used in the economic analysis
The summary benefit measure used in the economic analysis was the number of new cases of NAIT detected. This was directly obtained from the cohort study. Discounting was not relevant.

Direct costs
The analysis of the costs was carried out from the perspective of the NHS. It included the costs of screening (blood samples and cord PLT count), antenatal ultrasound and midwife visit. The unit costs were presented separately from the resource quantities for most items. The resource use data were obtained from the sample of women included in the effectiveness analysis. The costs were estimated using detailed costing systems (although these were not reported clearly) and published studies. Discounting was not relevant since the costs were incurred during a short timeframe. The costs were estimated using 2003/04 prices.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not considered.

Currency
UK pounds sterling (£). UK costs were converted into US dollars ($) using a mean exchange rate for 2003 of 1 = $1.63.

Sensitivity analysis
A univariate sensitivity analysis was performed to assess the robustness of cost-effectiveness ratios to variations in the
cost of HPA-1 phenotyping, genotyping and HPA-1a alloantibody tests. The sources of the alternative values were not stated.

**Estimated benefits used in the economic analysis**

The number of new cases of NAIT (<150 ×10^9/L) detected was 3 with no screening and 8 with both antenatal screening strategies.

The number of new cases of severe NAIT (<50 ×10^9/L) detected was 3 with no screening and 5 with both antenatal screening strategies.

**Cost results**

The total costs was 0 with no screening, 123,748 ($201,710) with antenatal screening that did not consider the development of alloantibodies, and 121,191 ($197,541) with antenatal screening that considered the development of alloantibodies.

**Synthesis of costs and benefits**

An incremental cost-effectiveness ratio (ICER; i.e. the incremental cost per NAIT case detected) was calculated to combine the costs and benefits of the alternative strategies under examination.

Antenatal screening that did not consider the development of alloantibodies was dominated by antenatal screening that considered the development of alloantibodies, and was thus excluded from further comparison. The ICER with antenatal screening that considered the development of alloantibodies over no screening was 24,238 ($39,509) for NAIT (defined as <150 ×10^9/L) and 60,596 ($98,771) for severe NAIT (defined as <50 ×10^9/L).

The sensitivity analysis showed that the cost-effectiveness ratios were influenced by variations in the cost estimates. Specifically, a 50% variation in the cost of phenotyping caused the ICER for NAIT to range from 16,114 to 32,363 ($26,266 to $52,752), and the cost per severe case of NAIT detected to range from 40,285 to 80,906 ($65,664 to $131,877).

A preliminary calculation of the incremental cost per case of ICH prevented and the incremental cost per life-year gained was carried out using published evidence. This showed that the incremental cost per case of ICH prevented with antenatal screening (assuming that detection allowed for successful intervention) was 1,151,323 ($1,876,656), and that the incremental cost per life-year gained was 43,600 ($71,067).

**Authors’ conclusions**

Antenatal screening was effective in detecting cases of (severe) neonatal alloimmune thrombocytopenia (NAIT) in pregnant women. However, given the low frequency of serious bleeding complications, the extra costs of antenatal screening should be balanced against the potential benefits and procedural risks.

**CRD COMMENTARY - Selection of comparators**

The authors stated that no screening was selected as the basic comparator because it represented the conventional approach in their country. Two different screening strategies were considered. You should decide whether this is a valid comparator in your own setting.

**Validity of estimate of measure of effectiveness**

The effectiveness analysis was based on a prospective cohort study. The use of a clinical trial would have been more appropriate because the random allocation of patients to study groups would have reduced the potential impact of selection bias. However, the authors pointed out that consecutive patients were included. Also, it should be noticed that one objective of the study was to assess the prevalence of the HPA-1a negative phenotype in the population and that a
Validity of estimate of measure of benefit
The summary benefit measure used in the primary analysis was disease-specific, thus it cannot be compared with the benefits of other health care interventions. The authors calculated the impact of the screening strategies on expected survival in a secondary analysis. Life-years were discounted at the recommended rate. The use of life-years as the summary benefit measure is more appropriate, and they are also comparable with the benefits of other diseases and interventions.

Validity of estimate of costs
The perspective adopted in the study was appropriate as all the relevant categories of costs were included in the analysis. Details of the unit costs and quantities of resources used were presented for most items, which enhances the possibility of replicating the analysis in other settings. There was limited information on the source of the costs, although most costs were derived from direct accounting systems. No statistical analyses of the costs were carried out, but the results of the sensitivity analyses were reported. The price year was reported, which will facilitate reflation exercises in other time.

Other issues
The authors reported the clinical results of other studies. The current findings were at the lower end of the published range for specific events (NAIT cases and ICH episodes). In addition, the results of some cost-effectiveness studies comparing screening options for NAIT versus no screening were also reported. The issue of the generalisability of the study results to other settings was not explicitly addressed and the analysis focused on the UK setting. Few sensitivity analyses were carried out, thus the external validity of the study was limited. The authors stated that, since the population considered in the study was predominantly Caucasian, the results of the analysis should be restricted to Caucasian pregnant women. Caution is therefore required when extrapolating the conclusions of the current analysis to other populations of pregnant women.

Implications of the study
The study results suggest that the question as to whether antenatal screening for NAIT represents good value for money is still open since the results of the current study did not permit a definitive conclusion on the cost-effectiveness of the screening strategy.

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