The cost-effectiveness of treatment for varicocele related infertility
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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
Four strategies for the treatment of varicocele-related infertility were examined. The strategies were:

- observation;
- varicocele repair followed by up to 3 cycles of in vitro fertilisation (IVF) if the couple did not conceive in the year after varicocelectomy;
- up to 3 cycles of gonadotropin superovulation and intrauterine insemination (IUI), followed by up to 3 cycles of IVF if IUI was unsuccessful; and
- up to 3 cycles of immediate IVF.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of infertile couples aged younger than 40 years, in whom varicocele was present with no other etiological factors and the male had at least 5 million spermatozoa/mL on semen analysis. Couples in which the male had azoospermia were not included.

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

Dates to which data relate
The effectiveness data were derived from studies published between 1979 and 1999. Some resource use data were gathered in 1998. The price year was 1998.

Source of effectiveness data
The effectiveness evidence was derived from a review of completed studies.

Modelling
A model was used to assess the clinical and economic outcomes associated with the four treatment strategies. The time horizon of the model was 30 months. Further details of the decision model were not provided.
Outcomes assessed in the review
The outcomes estimated were:

the probability of live delivery with observation, varicocelectomy, each cycle of gonadotropins plus IUI, and each IVF cycle;

the probability of stimulation failure or complication with each IVF cycle;

the probability of singleton birth if pregnant after observation or varicocelectomy, after IUI, or after IVF;

the probability of multiple gestation after IUI and after IVF; and

if multiple gestation, the probability of twins after observation or varicocelectomy.

Study designs and other criteria for inclusion in the review
A review of the literature was carried out using specific keywords. One of the primary studies was a review of the literature, while another was a publication from the Center for Disease Control. No information on the designs of the other primary studies was given.

Sources searched to identify primary studies
MEDLINE was searched from 1995 to 2000 using the keywords "varicocele" and "varicocelectomy". MEDLINE was also searched from 1990 to 2000 to assess the effectiveness of IUI using the keywords "intrauterine", "insemination" and "male factor infertility" or "varicocele". In addition, a published review of the literature was used to assess the effectiveness of varicocelectomy.

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

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

Number of primary studies included
Nine primary studies were included in the review.

Methods of combining primary studies
The primary estimates were combined by calculating the weighted averages.

Investigation of differences between primary studies
Not stated.

Results of the review
The probability of live delivery was 0.144 (range: 0.1 - 0.225) with observation, 0.297 (range: 0.144 - 0.6) with varicocelectomy, 0.119 (range: 0.037 - 0.349) with each cycle of gonadotropins plus IUI, and 0.254 (range: 0.05 - 0.6) with each IVF cycle.

The probability of stimulation failure or complication with each IVF cycle was 0.129 (range: 0.094 - 0.223).

The probability of a singleton birth if pregnant was 0.99 (range: 0.95 - 0.995) after observation or varicocelectomy.
0.79 (range: 0.69 - 0.95) after IUI, and 0.614 (range: 0.579 - 0.788) after IVF.

The probability of multiple gestation was 21% (range: 5 - 31) with IUI and 39% after IVF.

For multiple gestation, the probability of twins was 1% after observation or varicocelectomy.

**Measure of benefits used in the economic analysis**
The summary benefit measure used was the success rate. This was defined as the rate of live delivery of any number of neonates, and was derived from the decision model.

**Direct costs**
Discounting was not relevant as the costs were incurred during a short timeframe. The unit costs for the procedures were presented, while the quantities of resource use were not explicitly reported. The health services included in the economic evaluation were varicocelectomy, evaluations and cycles of IUI and IVF, the treatment of complications, and delivery-associated expenses (depending on the number of neonates). The costs of varicocelectomy covered preoperative evaluation and operative fees of the urologist and anaesthesiologist, outpatient hospital costs, and laboratory costs. Costs for IUI and IVF related to professional charges, medications, and laboratory and imaging testing. The cost/resource boundary of both the health care payer and the patient was considered in the analysis. The costs were estimated using data derived from published studies for multiple gestational pregnancies, and using Medicare reimbursement rates and local providers for other categories of costs. The resource data were mainly based on authors’ assumptions and some published series of patients. All the costs were updated to 1998 values using the medical care component of the Consumer Price Index.

**Statistical analysis of costs**
The costs were treated deterministically in the base-case.

**Indirect Costs**
The indirect costs were not considered in the economic evaluation.

**Currency**
US dollars ($).

**Sensitivity analysis**
Univariate sensitivity analyses were carried out on all model inputs, so as to assess the robustness of the estimated cost-effectiveness ratios. The ranges of values used were derived from the literature (probability values).

**Estimated benefits used in the economic analysis**
The success rate was 14% with observation, 72% with varicocelectomy-IVF, 73% with IUI-IVF, and 61% with immediate IVF.

**Cost results**
From the perspective of the health care payer, the estimated per patient costs were $1,996 with observation, $32,171 with varicocelectomy-IVF, $36,322 with IUI-IVF, and $39,001 with immediate IVF.

From the perspective of the patient, the estimated per patient costs were $0 with observation, $15,980 with varicocelectomy-IVF, $16,149 with IUI-IVF, and $20,394 with immediate IVF.
Synthesis of costs and benefits

The average and incremental cost-effectiveness ratio was calculated to combine the costs and benefits of the treatment strategies.

From the perspective of the health care payer, the average cost per live delivery was $13,863 with observation, $44,522 with varicocelectomy-IVF, $49,757 with IUI-IVF, and $64,422 with immediate IVF. The incremental cost per additional live delivery was $52,152 with varicocelectomy-IVF over observation, $561,423 with IUI-IVF over varicocelectomy-IVF, while immediate IVF was dominated by IUI-IVF and varicocelectomy-IVF.

From the perspective of the patient, the average cost per live delivery was $0 with observation, $22,114 with varicocelectomy-IVF, $22,122 with IUI-IVF, and $33,686 with immediate IVF.

The incremental analysis showed that both varicocelectomy-IVF and immediate IVF were dominated. The incremental cost per additional live delivery was $27,371 with IUI-IVF over observation.

The sensitivity analysis showed that the ranking of the alternative strategies was generally not affected by changes in the baseline inputs. There were two exceptions. First, when the probability of live delivery with varicocelectomy was below 22.3%, IUI-IVF became the preferred strategy. Second, when the probability of live delivery per IUI cycle was below 17.6%, then varicocelectomy-IVF became the preferred strategy.

Authors’ conclusions

Varicocelectomy followed by in vitro fertilisation (IVF) represented the most cost-effective strategy from the perspective of the payer/insurer, while intrauterine insemination (IUI) followed by IVF was the most effective approach from the perspective of the patients. A striking result of the analysis was that the most technologically advanced infertility treatment (i.e. immediate IVF) was not a cost-effective strategy. These conclusions were robust to a wide range of variations investigated in the sensitivity analysis.

CRD COMMENTARY - Selection of comparators

The selection of the comparators appears to have been appropriate, as it included widely used approaches for the treatment of varicocele-related infertility. The authors noted that the strategy of varicocelectomy followed by IUI was not considered because of the paucity of data, and also because this could have introduced some temporal incomparability. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness

The analysis of effectiveness was based on a review of the literature. Some of the methods and conduct of the review were reported. However, there was very limited information on the design of the primary studies. The primary estimates were combined by calculating the weighted averages. The extreme values observed in the literature were then used as ranges of variation in the sensitivity analysis.

Validity of estimate of measure of benefit

The summary benefit measure was specific to the interventions considered in the study and represents a widely used benefit for infertility treatments. However, it would probably be difficult to compare with the benefits of other health care interventions. The measure was obtained from a decision model that was not explicitly described. The authors acknowledged that their definition of success was somewhat narrow. Similarly, the future pregnancies potentially resulting from successful varicocelectomy were not considered.

Validity of estimate of costs

The analysis of costs was carried out from two different perspectives, which were appropriate since in several health care systems the patients have to pay for infertility treatment. Unit costs were presented only as macro-categories. The price year was reported, which will simplify reflation exercises in other settings. The cost estimates were varied in the
sensitivity analyses and the results were fairly robust to variations in economic parameters. The source of the data was reported.

Other issues
The authors compared some of their findings with those from other studies that reported controversial results. The issue of the generalisability of the study results to other settings was not addressed, which reduces the external validity of the analysis. The authors noted some limitations of their analysis, which have been reported already. The study referred to varicocele-related infertility and this was reflected in the conclusions of the analysis.

Implications of the study
Decision-makers, patients, insurers, and providers should be aware that immediate IVF does not represent good value for money to treat varicocele-related infertility. Other approaches, such as varicocelectomy and IUI (both followed by IVF if unsuccessful), could represent more cost-effective strategies.

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Other publications of related interest


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