Cost-effectiveness of treatments for dysfunctional uterine bleeding in women who need contraception
Blumenthal P D, Trussell J, Singh R H, Gao A, Borenstein J, Dubois R W, Liu Z

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 examined several treatments for dysfunctional uterine bleeding (DUB) in women requiring contraception. The treatments were oral contraceptives (OCs), the levonorgestrel-releasing intrauterine system (LNG-IUS) and surgical management. Surgical management included first-generation (transcervical resection, roller-ball and laser) and second-generation (thermal balloon, microwave, radiofrequency, cryoablation and hydrothermal) endometrial ablation techniques, as well as hysterectomy (vaginal, abdominal and laparoscopic assisted).

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population included a hypothetical cohort of women with DUB who did not wish to have children.

Setting
The setting was a hospital and 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 1991 and 2005. No dates for the resource use data were explicitly reported. The price year was 2005.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies and authors' opinions.

Modelling
A Markov model with a time horizon of 5 years was constructed to simulate the clinical and economic outcomes in a hypothetical cohort of eligible women receiving the alternative treatments examined in the study. Initially, women had a 3-month trial of OCs in accordance with current guidelines. Those who failed OCs were called initial OC non-responders, while those who succeeded with OCs were called initial OC responders. The analysis was performed under each of the three scenarios described above. Thus, three analyses based on Markov chains were carried out. Women could stay on the current treatment option or move to another treatment strategy depending on the combined results from contraception and treatment of DUB (either success or failure). For example, women who failed medical therapy after long-term use underwent a second diagnostic workup (with hysteroscopy and endometrial biopsy) before proceeding to surgical management. The cycle length of the Markov model was not reported explicitly but it might have

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been 1 year. A schematic representation of the model was provided.

Outcomes assessed in the review
The outcomes estimated from the review of the literature were the DUB success rates and rates of contraceptive failure associated with OCs, LNG-IUS, endometrial ablation and hysterectomy. The DUB success rate was defined as a post treatment pictorial blood loss assessment score (PBAC) of 75 or lower, corresponding to a blood loss of less than 60 mL. The proportions of women undergoing ablation or hysterectomy after medical therapy failure were also reported.

Study designs and other criteria for inclusion in the review
A systematic review of the literature was undertaken to identify English-language studies on the management of DUB that had been published between January 1990 and April 2005. The review included only articles that reported the outcomes of interest associated with OCs, the LNG-IUS, ablation and hysterectomy. Only comparative studies were included, thus case series and case studies were excluded. Most of the evidence came from randomised clinical trials. In particular, the DUB success rate was obtained from one clinical trial for OCs, two for LNG-IUS and eleven for surgical management. However, little information on the design and other characteristics of these primary studies was provided.

Sources searched to identify primary studies
MEDLINE, EMBASE, HealthSTAR and Cochrane databases were searched. The keywords used were "menorrhagia", "dysfunctional uterine bleeding", "heavy menstrual bleeding", "abnormal uterine bleeding", "LNG-IUS", "levonorgestrel-releasing intrauterine system", "IUS", "oral contraceptive pills", "OC", "oral contraceptive", "OCP", "endometrial resection", "endometrial ablation", "hysterectomy", "contraception" and "contraceptive". The bibliographies of the retrieved articles were also checked.

Criteria used to ensure the validity of primary studies
Much of the clinical evidence on treatment efficacy came from clinical trials. This should ensure a high internal validity.

Methods used to judge relevance and validity, and for extracting data
Appropriate data abstraction was ensured by independent dual review.

Number of primary studies included
Twenty-five primary studies provided the evidence.

Methods of combining primary studies
DUB success rate for LNG-IUS was the average of the results of two clinical trials, while DUB success rate for ablation techniques was the median of the clinical trials used in order to mitigate the effect of studies with outlier success rates.

Investigation of differences between primary studies
The authors stated that the population varied across the studies and was not always comparable.

Results of the review
The DUB success rate was 37.5% (range: 37.5 to 73.0) with OCs, 66.0% (range: 57.0 to 88.0) with the LNG-IUS, 78.4% (range: 67.4 to 96.0) with endometrial ablation and 100% with hysterectomy.

The rate of contraceptive failure was 8.0% with OCs, 0.1% with the LNG-IUS, 0.7% (range: 0.2 to 1.6) with endometrial ablation and 0% with hysterectomy.
The distribution of contraceptive failures was as follows:

- with OCs, ectopic pregnancy 0.010, induced abortion 0.501, spontaneous abortion 0.123 and birth 0.366;
- with the LNG-IUS, ectopic pregnancy 0.600, induced abortion 0.202, spontaneous abortion 0.050 and birth 0.148;
- with endometrial ablation, ectopic pregnancy 0, induced abortion 0.471, spontaneous abortion 0.107 and birth 0.422.

The proportions of women undergoing ablation and hysterectomy after medical therapy failure were 50% and 50%.

**Methods used to derive estimates of effectiveness**
The authors made some assumptions that were used in the decision model.

**Estimates of effectiveness and key assumptions**
The long-term success rate for OCs was assumed to be the same as that observed over the short-term (37.5%).

The annual failure rate (among those who initially succeeded) associated with the LNG-IUS and ablation was assumed to be 10%.

**Measure of benefits used in the economic analysis**
The summary benefit measure was the effectiveness of treatment. This was based on a combination of DUB treatment and contraception success. It was estimated using the modelling approach. No discounting was applied.

**Direct costs**
The analysis took the viewpoint of the third-party payer and included the costs associated with drugs, devices, a second diagnostic workup, surgical procedures, office visits and hospitalisation. The unit costs and the quantities of resources used were presented separately for most items. The estimation of costs was based on average wholesale prices, Medicare reimbursement rates and some published studies. The base-case analysis did not include side effects, owing to their low incidence, although they were included in the sensitivity analysis. Limited information on the sources of resources use was provided. Discounting was relevant, as long-term costs were incurred, and an annual discount rate of 3% was used. The price year was 2005.

**Statistical analysis of costs**
The costs were treated deterministically.

**Indirect Costs**
Indirect costs were not included as they were not relevant to the perspective adopted in the analysis.

**Currency**
US dollars ($).

**Sensitivity analysis**
Deterministic one-way sensitivity analyses were carried out to assess the robustness of the cost-effectiveness results to variations in the model inputs. The model inputs investigated included the success rate, definition of effectiveness based exclusively on DUB success, time to first surgery, inclusion of costs associated with the management of adverse events, the probability of finding structural abnormalities after a second diagnostic workup, the proportion of women choosing ablation over hysterectomy, and the proportion of women choosing to live with DUB after medical therapy or surgery.
failure. Alternative values were derived from published studies or the authors' opinions. For example, the costs were arbitrarily varied by +/- 20%.

**Estimated benefits used in the economic analysis**
All model outputs were reported at different time horizons (1, 2 and 5 years).

In the group of OC non-responders, the success rates with LNG-IUS and surgery were, respectively, 72.7% and 88.9% at 1 year, 91.1% and 94.1% at 2 years, and 92.0% and 95.5% at 5 years.

In the group of OC responders, the success rates with LNG-IUS and OCs were, respectively, 72.7% and 46.0% at 1 year, 91.1% and 81.8% at 2 years, and 92.0% and 90.4% at 5 years.

In the group of patients naive to medical therapy, the success rates with LNG-IUS first-line and OCs first-line were, respectively, 72.7% and 72.8% at 1 year, 91.1% and 89.5% at 2 years, and 92.0% and 93.6% at 5 years.

**Cost results**
In the group of OC non-responders, the total costs per patient with LNG-IUS and surgery were, respectively, $742 and $3,360 at 1 year, $1,696 and $3,900 at 2 years, and $2,796 and $4,853 at 5 years.

In the group of OC responders, the total costs per patient with LNG-IUS and OCs were, respectively, $742 and $866 at 1 year, $1,696 and $2,763 at 2 years, and $2,796 and $4,711 at 5 years.

In the group of patients naive to medical therapy, the total costs per patient with LNG-IUS first-line and OCs first-line were, respectively, $742 and $2,520 at 1 year, $1,696 and $3,569 at 2 years, and $2,796 and $4,895 at 5 years.

**Synthesis of costs and benefits**
Incremental cost-effectiveness ratios were calculated in order to combine the costs and benefits of the alternative strategies.

In the group of OC non-responders, the incremental cost per additional success with surgery over LNG-IUS was $16,163 at 1 year, $73,952 at 2 years, and $59,567 at 5 years.

In the group of OC responders, LNG-IUS dominated OCs, which were both less effective and more expensive.

In the group of patients naive to medical therapy, the incremental cost per additional success with OC first-line over LNG-IUS first-line was $1,755,462 at 1 year and $137,621 at 5 years, while LNG-IUS dominated OCs at 2 years.

The results of the sensitivity analysis showed that the base-case results were robust to changes in model assumptions. Small variations were achieved when assuming 20% of women undergo surgery at 6 to 12 months after the beginning of medical therapy; including costs associated with adverse events; and varying the probability of finding structural abnormalities after a second diagnostic workup from 20% to 0%. These variations further favoured the LNG-IUS strategy. Slightly better results for the surgical option were observed if it was assumed that 10% of women chose to live with DUB after medical therapy or ablation/repeat ablation failure. Finally, if a higher proportion of women chose ablation over hysterectomy, the cost-effectiveness of LNG-IUS improved.

**Authors' conclusions**
The levonorgestrel-releasing intrauterine system (LNG-IUS) was the most cost-effective treatment for women with dysfunctional uterine bleeding (DUB) who needed contraception in the USA. The LNG-IUS was cost-saving and more successful than oral contraceptives (OCs) among OC responders, was more cost-effective than surgery among OC non-responders (very high incremental ratios for surgery over LNG-IUS), and was more cost-effective than OCs in women naive to medical therapy.
CRD COMMENTARY - Selection of comparators
The authors justified the choice of the comparators, which were appropriately selected. Progestogens and other hormonal therapies were excluded from the comparison because they are less effective or not suitable for long-term use. In addition, non-hormonal therapies that did not offer contraceptive benefits, such as non-steroidal anti-inflammatory drugs or antifibrinolytics, were not relevant comparators. You should decide whether the chosen comparators are valid in your own setting.

Validity of estimate of measure of effectiveness
The effectiveness evidence was obtained from a systematic review of the literature, and the methods and conduct of the review were reported. For example, the authors reported the search criteria and inclusion criteria, and an appropriate data extraction was carried out. The inclusion of clinical trials should have ensured the robustness of the primary estimates. In general, the authors did not provide much detail on, for example, the number and type of patients involved or the length of follow-up. The issue of heterogeneity amongst the primary estimates was not explicitly addressed, although it was noted that study populations varied across studies and were not always comparable. The authors carried out extensive sensitivity analyses to investigate the uncertainty surrounding some clinical estimates or model assumptions.

Validity of estimate of measure of benefit
The summary benefit measure was specific to the disease considered in the study. Therefore, it will not be possible to compare it with the benefits of other health care interventions. The authors acknowledged that the benefit was an intermediate measure and an alternative definition of treatment effectiveness was used in the sensitivity analysis. However, it was noted that the use of a measure incorporating health-related quality of life would have been more appropriate.

Validity of estimate of costs
The analysis of the costs was consistent with the perspective that was explicitly stated. The authors stated that the inclusion of indirect costs would have been interesting but would not have changed the results of the analysis. The sources used to derive the costs reflected the viewpoint of the third-party payer. However, limited information on the sources of resource consumption was provided. Details of the unit costs and quantities of resources used were presented for most items, which will assist when replicating the analysis in other settings. Statistical analyses of the costs were not performed, but the cost estimates were varied in the sensitivity analysis. The price year was appropriately reported, which will facilitate reflation exercises in other time periods.

Other issues
The authors stated that their findings were consistent with those from other published studies. The issue of the generalisability of the study results to other settings was not explicitly reported, although the extensive use of sensitivity analysis enhances the external validity of the analysis. However, the results of the sensitivity analyses were presented selectively. Some limitations of the study were also highlighted. Specifically, the use of multiple and different sources to derive clinical inputs represents an issue common to all modelling approaches. Another point was the fact that the study did not make a distinction between first- and second-generation ablation techniques. In practice, second-generation procedures should be less expensive and safer. Overall, the analysis provided conservative results given that most assumptions biased the analysis in favour of surgical procedures. The study referred to the general population of women with DUB without differentiating women by age. However, in reality, the choice of the procedures and the outcomes associated with these interventions could differ depending on the age of the patient. The authors noted that this issue was partially offset by considering women who do not desire future pregnancies.

Implications of the study
The study results supported the use of the LNG-IUS for the treatment of DUB women who do need contraception. The authors stated that future studies should incorporate different ages and different patient choices.
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