Comparison of Levonorgestrel-releasing Intrauterine System (LNG-IUS) against Laparoscopic Assisted Supracervical Hysterectomy (LASH) for menorrhagia treatment: an economic evaluation

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Abstract

Objective: To compare the cost-effectiveness of laparoscopic assisted supracervical hysterectomy (LASH) with NICE's gold-standard treatment of Levonorgestrel-releasing intrauterine system (LNG-IUS) for menorrhagia treatment. Design: Economic evaluation. Setting: European studies. Population: Women under 50 referred for surgical menorrhagia treatment and eligible for endometrial ablation. Methods: A cost-utility analysis was conducted from an NHS perspective using data from existing literature to compare the treatments. Individual costs and benefits were assessed within one year of having interventions. An Incremental Cost-Effectiveness Ratio (ICER) was calculated, followed by sensitivity analysis. Main Outcome Measures: Expected Quality Adjusted Life Years (QALYS) and costs to the NHS were calculated alongside health net benefits (HNB) and monetary net benefits (MNB). Results: An ICER of 0.7 was used to calculate a MNB between -£14.99 and -£714.99, coupled with a HNB between –0.0357 QALYs and –0.0005 QALYS. LNG-IUS was more cost-effective than LASH, with LASH exceeding the upper bound of the £30,000/QALY limit used by NICE. Sensitivity analysis lowered the ICER below the given threshold. Conclusions: The ICER demonstrates it would not be cost-effective to replace the current gold-standard LNG-IUS with LASH, when treating menorrhagia in the UK. The ICER's proximity to the threshold and its high sensitivity alludes to the necessity for further research to generate a more reliable cost-effectiveness estimate. Funding: None. Keywords: Economic evaluation, Cost-utility analysis, Incremental cost-effectiveness ratio (ICER), Levonorgestrel-releasing intrauterine system (LNG-IUS), Laparoscopic assisted supracervical hysterectomy (LASH), Menorrhagia. Tweetable abstract: LNG-IUS is marginally more cost-effective than LASH as a gold standard treatment for menorrhagia.

1. Introduction

1.1 Background

Menorrhagia is menstrual blood loss of more than or equal to 80mL[1]. Accurately quantifying menstrual blood loss is difficult and depends on an individual's personal experience. Therefore, menorrhagia can also be classified as excessive volume or duration i.e. lasting more than 7 days[2]. Despite approximately 50% of women not finding a cause for their heavy menstrual bleeding, underlying conditions may be present in some women, such as uterine fibroids, or systemic conditions such as hypothyroidism[1].

Management of menorrhagia is dependent on the presence of an underlying cause. In patients where there is no identifiable condition or where fibroids less than 3cm are found, first-line treatment is insertion of the levonorgestrel-releasing intrauterine system (LNG-IUS)[1], releasing progestogens thickening the uterus lining[3].

If this is unsuitable, non-hormonal or surgical treatments may be considered[1]. Surgical options include endometrial ablation or a hysterectomy[3]. LNG-IUS is the preferred evidence-based first line intervention, demonstrating higher efficacy than non-hormonal treatment, whilst also being less invasive and costly than surgery[4]. It also allows for preservation of fertility[4].

1.2 Motivation and rationale

Menorrhagia is common in England and Wales[5]. In 2019, it was reported that 25% of women of reproductive age were affected by menorrhagia with approximately 28,000 women undergoing surgical intervention annually[5]. With great impacts on a woman's physical, emotional, social and material quality of life[6], it is important to reduce these effects.

In the UK, 5% of women aged 30-49 will access their GP due to menorrhagia[7]. With an average GP appointment costing the NHS £30[8], and the total number of women aged between 30-49 in 2018 being 8,740,316[9], this translates to 437,016 women consulting their GP annually, generating a total cost of £13,110,474 to the NHS. It is vital for the NHS to provide the most cost-effective treatments to this large patient cohort.

1.3 Objectives

As aforementioned, first-line treatment for menorrhagia is insertion of the LNG-IUS[1], however, resultant long-term effects mean many women require surgery after discontinued LNG-IUS use[10]. A novel surgical technique for menorrhagia treatment is laparoscopic assisted supracervical hysterectomy (LASH), a type of hysterectomy leaving the cervix in situ. LASH reduces operating time and reduces mortality from surgery[11]. Therefore, we aimed to compare the cost-effectiveness of this new technique with the current gold-standard treatment.

2. Methods

2.1 Literature Search

A search of the databases PubMed, Embase and Google Scholar demonstrated that no cost-utility analysis comparing LASH and LNG-IUS had been completed globally.

There has been comprehensive literature comparing various treatments for menorrhagia. Current literature varies in which treatments lead in cost-effectiveness, with both hysterectomy[12] and LNG-IUS[13,14,15] having better outcomes as well as reporting of no significant difference[16], despite a vast disparity in costs. However, systematic analysis of the literature[4] has shown very little difference in clinical effectiveness or patient satisfaction between treatment options.

An extensive literature search highlighted two UK-based randomised controlled trials in which cost-utility analyses of LASH and LNG-IUS had been conducted with different comparators. One was sourced from the Lancet[11], comparing LASH to endometrial ablation. The other compared LNG-IUS with standard medical treatment and was published in the Health Technology Assessment Journal[10], which is used to inform NICE guidance. Accordingly, both represent reputable sources for the analysis. These studies were used to obtain the majority of costs, probabilities and QALYs values, whilst the remainder were obtained from the NHS and other reliable UK studies.

2.2 Funding

No funding was needed for this study.

2.3 Choice of perspective and analysis

For this economic analysis, the NHS perspective was chosen in relations to costs, utility and probability values. This evaluation was conducted to help maximise the limited NHS budget and guide effective resource allocation. As health outcomes were determined in terms of quality of life, rather than monetary values, a cost-utility analysis was conducted.

To determine outcomes, Quality-Adjusted Life Years (QALYs) are calculated. QALYs measure the health state of an individual, considering the extra length of life one can benefit from an intervention whilst adjusting for the quality of their life during this period.

In the primary literature sources, quality of life was assessed through use of the EQ-5D questionnaire. This looks at five different aspects of health: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. With heavy menstrual bleeding impacting several diverse aspects of a woman's life, the EQ-5D provides a holistic overview of this impact. Furthermore, this is in line with NICE recommendations on measuring health-related quality of life in adults, as EQ-5D scores ensure consistency and are easily calculated into QALYs[17].

2.4 Choice of Horizon and Justification

To conduct the cost-utility analysis, individual costs and benefits were assessed within one year of having the intervention. The rationale behind this is that at one-year post LNG-IUS insertion, menstrual bleeding has been shown to reduce by up to 96%[18] with benefits mainly observed after six months[19]. This represents a significant proportion of women for whom the condition is stabilised and so supports focusing on outcomes during the first year. Additionally, LNG-IUS treatment failure is assumed to be more evident in the first year further supporting a one-year time horizon[12].

Outcomes were analysed 15 months post-randomisation for LASH as it allows for an approximate three-month waiting list period between randomisation of the surgery and the actual intervention. This is in line with the Scottish and UK government guidelines. Furthermore, the majority of costs associated with the surgical intervention occur within the first year[11], hence the appropriateness of a one-year time horizon.

2.5 Decision tree

LASH and LNG-IUS offer two inherently different ways of treating menorrhagia. Due to LASH being a surgical intervention and the LNG-IUS a medical device, the patient pathways within the decision tree vary based on the alternative outcomes each procedure can bring. Each branch arising from the complications or LNG-IUS discontinued decision nodes are derived from the reported adverse effects within the studies[10,11]. The probabilities for each of these were calculated from the overall study size and the prevalence of each side effect within the cohort.

Within the LASH group, there were multiple varied complications only experienced by one individual each within the study. For this evaluation, we decided to group these into the "Other" branch and take the worst-case scenario of these amalgamated events. The expected values at each stage of the tree were calculated through the sum of each terminal branch.

The completed decision tree can be seen in figure 1.

2.6 Costs

Costs for this analysis have been calculated as incurred from the NHS perspective. Thus, any external societal costs or patient costs have been excluded. The majority of these have been sourced from the two original studies this evaluation is based on. Calculation of the remaining costs were derived from appropriate literature. A brief cost breakdown is included below. All costs were discounted or inflated to 2011 levels, using a 3.5% discount rate in line with NICE guidance[20].

LASH No Complications

The total cost of the LASH operation includes anaesthesia and operating theatre use costs, staffing costs and the overall cost of hospital stay. This total cost excluded any complication costs and was discounted from the 2017 value to generate an overall figure, at 2011 levels.

LASH Complications

The majority of these costs have been sourced from the literature, as individual costs of each complication were not present within the original studies. The "Other" branch is a collection of complications which each occurred in one patient only. To calculate the cost for this branch, the most expensive complication, bladder injury, was used. The individual cost of each complication was added to the original cost of carrying out the LASH operation in order to calculate an overall figure.

LASH Failure

In the one case of LASH failure, the operation was converted to a full hysterectomy which is associated with a higher utility[21]. In this case, the additional time of 80 minutes[21] required for the completion of the procedure was added to the original cost of the LASH operation. This was based upon the hourly cost of operating theatre use and staffing[11].

LNG-IUS

The ECLIPSE study provided the cost for successful LNG-IUS treatment which comprised of the initial consultation, insertion and follow-up costs[10]. These costs were given in 2011 values, meaning no discounting was required.

LNG-IUS Complications

Complication costs mainly consisted of the original cost of insertion, but also included the cost of LNG-IUS discontinuation. In some cases, it was assumed additional GP appointments were required regarding advice on side effects and prescription of medications needed to manage these. Cost of such medications/equipment was included, alongside the cost of appointments. This is particularly true in the case of discontinuation due to bleeding, where STI and pregnancy testing are first-line investigations, so these costs were included[22,23,24].

LNG-IUS Failure

In the case of LNG-IUS insertion failure, it was assumed patients would subsequently attempt another intervention. The cost of each of these was calculated using the ECLIPSE study[10] or other literature[25,26]. For the pharmacological treatment branch, it was assumed that patients had the most common treatment option of tranexamic and mefenamic acid[10].

2.7 Benefits

QALY calculation

In this evaluation, QALY scores were used in order to assess the utility of the patients for each branch of the decision tree. This is calculated as:

Quality of Life (QOL) x Length of Life (LOL) = QALY

As the time horizon for this economic evaluation is set at one year, the QALY score is simply:

QOL x 1 = QALY

QOL scores were sourced from the two original studies (HEALTH and ECLIPSE), and where necessary, the literature was reviewed and other QOL measures were found.

QALY scores

As most of the complications analysed were short-term, it was assumed that these would resolve completely within one year. Hence, the QALYs of the patients experiencing these complications are modelled to be the same as those who had a successful treatment, particularly with LASH. Overall, this means no discounting of QALYs was required.

For LNG-IUS use, patients had more varied utility outcomes. These ranged from those who returned to pre-treatment utility due to treatment discontinuation and those who experienced a lower quality of life than that of just menorrhagia. This lower utility is due to more severely impacting side effects, such as

depression or pain, which led to LNG-IUS discontinuation after six months. For the latter, we consulted relevant literature to determine the reduction in QALYs people with these conditions experience[27,28] and combined it with a six month utility of pre-treatment levels, to calculate their overall utility.

3.Results

3.1 Incremental Cost-Effectiveness Ratio (ICER)

The ICER for the LASH against LNG-IUS treatment is seen in figure 2.

The ICER calculation is as follows:

ΔCost/ΔUtility = (£2,427.27-£312.28)/(0.840-0.770) = £2,114.99/0.070 = £30,214/QALY

3.2 Monetary Net Benefit (MNB) and Health Net Benefit (HNB)

MNB and HNB both compare the difference in cost and utility within the context of a maximum willingness to pay (Rc). For either of these measures, if the calculated value is larger than zero then the treatment can be viewed as cost effective.

MNB = (Rc* [?]E)- [?]C = (PS30,000*0.070)-PS2,114.99 = -PS14.99

MNB = (Rc* [?]E)- [?]C =(PS20,000*0.070)-PS2,114.99 = -PS714.99

HNB = [?]E- [?]C/Rc = 0.070-PS2,114.99/PS30,000 = -0.0005 QALY

HNB = [?]E- [?]C/Rc = 0.070-PS2,114.99/PS20,000 = -0.0357 QALY

These calculations demonstrate a monetary net benefit between -PS14.99 and -PS714.99, which, coupled with a health net benefit between –0.0357 QALYs and –0.0005 QALYS, reinforce current NICE guidelines that LNG-IUS treatment should be first line in women with heavy menstrual bleeding.

As the ICER is 0.7% above the higher recommended NICE threshold, a sensitivity analysis is vital to determine if the ICER changes, and thus our interpretation.

3.3 Sensitivity analysis

A sensitivity analysis was conducted due to uncertainty in various factors used in the economic evaluation[29]. Sensitivity analyses enable the consideration of a wide range of scenarios and thus increases confidence in the model proposed[29]. In this evaluation, one-way sensitivity analyses were conducted, in which one parameter was altered with others unchanged to assess the resultant effects on the ICER.

The first sensitivity analysis explores costs changes to the "Other" complication branch. Utility for both cases remains identical due to the short-term nature of these complications. Changing this to the best-case scenario, a pain consultation, gives a new ICER of:

ΔCost/ΔUtility=(£2,279.32-£312.28)/(0.840-0.770)= £1,967.04/0.070=£28,101/QALY

In the literature, there are a variety of statistics for LNG-IUS insertion failure rate with one Swedish paper[30]stating a different rate of 1.68%. In this second sensitivity analysis, the new ICER is:

ΔCost/ΔUtility=(£2,427.27-£290.14)/(0.840-0.757)= £2,137.13/0.083=£25,749/QALY

4. Discussion

4.1 Main findings

The ICER calculated demonstrates that it would not be cost effective to replace the current gold-standard LNG-IUS treatment with LASH. This is due to it exceeding the upper bound of the £30,000/QALY limit that the NHS and NICE operate within by £214.

Due to the proximity of the ICER to the NICE threshold, sensitivity analysis is key to considering the implementation of LASH as a new first line treatment. The analysis carried out demonstrated high levels of

sensitivity, as the ICER dropped below the given threshold after altering various parameters. Considering the accuracy of costs, probabilities and QALYs used is integral to acceptance or rejection of this treatment, and additional research in this area needs to be carried out in order to further explore this.

A further factor to consider is the time horizon used for this evaluation. A one-year time horizon was utilised due to the stability of menorrhagia for most in this timeframe. Whilst the majority of LASH complications were short term, some of the LNG-IUS side effects may still occur at much later timeframes[30], which would be likely to impact the expected costs and QALYs of this treatment arm negatively.

On the other hand, the relatively small raw QALY increase of 0.070 gives context to whether the increased cost is worthwhile. It questions if the additional costs and complications are justifiable for such a small gain in QOL.

4.2 Strengths and Limitations

The main strengths of the analysis was the comprehensive literature search undertaken to ensure cost and benefit values used were most relevant. All costs were derived from the HEALTH and ECLIPSE studies, and any other missing costs were acquired from other relevant Randomised Control Trials, ensuring a complete and thorough analysis was conducted. Furthermore, this cost-utility analysis is original and has not been previously conducted which means the findings are relevant and have potential to influence current guidelines. Finally, the methodology used was robust with extensive consideration of complications and side-effects of treatment to ensure an accurate ICER was calculated.

The main limitation of the analysis was the lack of consideration of treatment acceptability by patients which limits the usefulness of the results. Additionally, the model assumes that side-effects/complications experienced are independent, whereas in reality patients may experience multiple complications. For LASH, the complications of very low prevalence were also grouped for simplicity.

Additionally, the baseline characteristics of the women included in the individual studies differed. In the HEALTH study, women with fibroids <3cm were included whilst in the ECLIPSE study, women with any sign of fibroids were excluded. Nonetheless, according to NICE, these women would still follow the same treatment pathway and therefore do not fully negate the results. Additionally, utility values for further treatment after initial intervention failure were sourced from other UK based studies[12] and the primary data sources[10]. Collectively, the sample baseline characteristics in other studies used differed from the initial studies and hence, utility values may not be comparable.

4.3 Interpretation

This is the first research worldwide to examine the cost-effectiveness of LNG-IUS compared to LASH in the management of menorrhagia. Similar studies in the US[13] and Finland[15]explored the cost effectiveness of LNG-IUS compared to hysterectomy. Both studies found LNG-IUS to be a more cost effective alternative to hysterectomy. However, these studies found LNG-IUS to be, in most cases, distinctively more cost-effective than hysterectomy. This study found a less significant cost-effectiveness to LNG-IUS when compared with LASH which may suggest that LASH could provide a more cost effective alternative to traditional hysterectomies.

5. Conclusion

Ultimately, LASH is not cost effective in comparison to the LNG-IUS for women with heavy menstrual bleeding. For results generalisation, the proximity of the ICER to the threshold and its high sensitivity alludes to the necessity for further research to generate more robust data, and thus a more reliable cost-effectiveness estimate. To conclude, for heavy menstrual bleeding, NICE should continue with the recommended gold standard treatment of LNG-IUS.

A crucial factor around challenging the first-line treatment for menorrhagia would be the feasibility regarding the provision of high surgical intervention volumes, and the use of hospital resources in an overstretched NHS surgical environment. Long waiting times may lead to the need for added short-term interventions to bridge

the lack of treatment during this period. These would have to be considered in the overall costs and utilities of LASH.

There is no current literature comparing the cost-effectiveness of LASH with LNG-IUS. The literature comparing generic hysterectomy against LNG-IUS is inconclusive regarding which intervention is more cost-effective. These results support other studies promoting the use of LNG-IUS over hysterectomy[13,14], though are not directly comparable due to the uniqueness of this research comparing LASH to LNG-IUS. This highlights the need for more research to be conducted directly comparing LASH to LNG-IUS.

A further factor is the inappropriateness of LASH for women wishing to maintain their fertility. For those with no desire of having children, LASH offers a one-time surgical intervention, opposed to on-going treatment, side-effects and their management which may occur with LNG-IUS use. Further research is required with consideration of a longer time horizon, as both costs to the patient and the NHS may influence the choices made around treatments. This gives implications to policy that women with no desire to have children should consider LASH as first-line treatment. Further research into the appropriateness of the costs and QALYs for the parameters used in the decision tree will help to steer future use of each of the treatments to ensure cost-effectiveness is optimised. Due to the close proximity of the ICER to the threshold value, it may be that different interpretations of these parameters notably impact the cost-effectiveness of LASH. Research into this, and the variation of the parameters in relation to other countries should be examined, in order to decide if results can be extrapolated into other regions or countries.

Conflict of interest: All authors report no conflict of interest.

Contribution: LM, PNC and DFM conceived the original idea. LM and PNC performed the analytic calculation and numerical simulation. LM and PNC took the lead in writing the manuscript with input from DFM, MS, FJ, ES. LM, PNC, DFM, MS, FJ, ES provided critical feedback, commented on the manuscript, made appropriate changes and gave final approval of the version to be published.

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