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Corresponding Author: Dr Lete Ignacio, MD

Corresponding Author's Institution: Hospital Santiago

First Author: lete ignacio

Order of Authors: lete ignacio; Ignacio Cristobal; Laia Febrer; Carlos Crespo; Agnes Arbat; Francisco J Hernandez; Max Brosa

Abstract: Objective: To compare the efficiency of the levonorgestrel-releasing intrauterine system (LNG-IUS) versus combined oral contraception (COC) and progestogens (PROG) in first-line treatment for dysfunctional uterine bleeding (DUB) in Spain.
Study Design: A cost-effectiveness and cost-utility analysis of LNG-IUS, COC and PROG was carried out using a Markov model based on clinical data from literature and expert opinion. The population studied were women with a previous diagnosis of idiopathic heavy menstrual bleeding. The analysis was performed from the National Health System perspective, discounting both costs and future effects at the 3%. In addition, a sensitivity analysis (univariate and probabilistic) was conducted.
Results: Results show that the greater efficacy of LNG-IUS translates into a gain of 1.92 and 3.89 symptom-free months (SFM) after 6 months of treatment, respectively, versus COC and PROG (which represents an increase of 33% and 60% of the symptom-free time). Regarding costs, LNG-IUS produces savings of 174.2-309.95 € and 230.54-577.61 € versus COC and PROG respectively, after 6 months-5 years. Apart from cost savings and gains in SFM, quality-adjusted life months (QALM) are also favourable to LNG-IUS in all scenarios, with a range of gains between 1 and 2 QALM compared to COC and PROG.
Conclusions: Results indicate that the first-line use of LNG-IUS is the dominant therapeutic option (less costly and more effective) in comparison with the first-line use of COC or PROG for the treatment of DUB in Spain. LNG-IUS as first line is also the option that provides greatest quality of life to patients.

Suggested Reviewers: Alicia Hernández Dr.
Hospital Universitario. La Paz, Madrid
jreyblas@hotmail.com

José Gutiérrez Dr.
Hospital Universitario Virgen de la Macarena, Sevilla

jgales@telefonica.net

Opposed Reviewers:

Dear Editor,

Enclosed is the manuscript "*Economic evaluation of the levonorgestrel-releasing intrauterine system for the treatment of dysfunctional uterine bleeding in Spain*" to be considered for publication in European Journal of Obstetrics & Gynecology and Reproductive Biology. I attest to the fact that all authors listed on the title page have read the manuscript, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission to European Journal of Obstetrics & Gynecology and Reproductive Biology .

Dr. Iñaki Lete Lasa

Gynaecology Department. Hospital Santiago Apóstol of Vitoria.

Olaguibel 29. 01004 Vitoria. Spain

Tel.: +34945007724 Fax: +34945007901

ilete@hsan.OSAKIDETZA.net

Economic evaluation of the levonorgestrel-releasing intrauterine system for the treatment of dysfunctional uterine bleeding in Spain

I[1] Lete, I[2] Cristóbal, L[3] Febrer, C[4,5] Crespo, A[6] Arbat, FJ[7] Hernández, M[4] Brosa

[1] Head of the Gynaecology Department. Hospital Santiago Apóstol. Vitoria. Spain

[2] Head of the Gynaecology and Obstetrics Department. Hospital Sanitas La Zarzuela. Madrid. Spain

[3] Health Economics, Outcomes & Reimbursement. Bayer HealthCare. Barcelona. Spain

[4] Oblikue Consulting. Barcelona. Spain

[5] Department of Statistics. University of Barcelona. Barcelona. Spain

[6] Medical Department, Bayer HealthCare. Barcelona. Spain

[7] Women's Health Unit, Bayer HealthCare, Barcelona. Spain

Address for correspondence:

Dr. Iñaki Lete Lasa

Gynaecology Department. Hospital Santiago Apóstol of Vitoria.

Olaguibel 29. 01004 Vitoria. Spain

Tel.: +34945007724 Fax: +34945007901

ilete@hsan.OSAKIDETZA.net

CONDENSATION

The first-line use of LNG-IUS is less costly and more effective in comparison with COC or PROG for the treatment of DUB in Spain.

ABSTRACT

Objective: To compare the efficiency of the levonorgestrel-releasing intrauterine system (LNG-IUS) versus combined oral contraception (COC) and progestogens (PROG) in first-line treatment for dysfunctional uterine bleeding (DUB) in Spain.

Study Design: A cost-effectiveness and cost-utility analysis of LNG-IUS, COC and PROG was carried out using a Markov model based on clinical data from literature and expert opinion. The population studied were women with a previous diagnosis of idiopathic heavy menstrual bleeding. The analysis was performed from the National Health System perspective, discounting both costs and future effects at the 3%. In addition, a sensitivity analysis (univariate and probabilistic) was conducted.

Results: Results show that the greater efficacy of LNG-IUS translates into a gain of 1.92 and 3.89 symptom-free months (SFM) after 6 months of treatment, respectively, versus COC and PROG (which represents an increase of 33% and 60% of the symptom-free time). Regarding costs, LNG-IUS produces savings of 174.2-309.95 € and 230.54-577.61 € versus COC and PROG respectively, after 6 months-5 years. Apart from cost savings and gains in SFM, quality-adjusted life months (QALM) are also favourable to LNG-IUS in all scenarios, with a range of gains between 1 and 2 QALM compared to COC and PROG.

Conclusions: Results indicate that the first-line use of LNG-IUS is the dominant therapeutic option (less costly and more effective) in comparison with the first-line use of COC or PROG for the treatment of DUB in Spain. LNG-IUS as first line is also the option that provides greatest quality of life to patients.

Key Words: Levonorgestrel-releasing intrauterine system; heavy menstrual bleeding; dysfunctional uterine bleeding; cost-effectiveness analysis; cost-utility analysis

INTRODUCTION

Dysfunctional uterine bleeding (DUB), defined as heavy menstrual bleeding (HMB) for several consecutive cycles in woman of child-bearing age[1], presents a high prevalence in western societies. In Spain, almost 20% of gynaecological visits are due to abnormal uterine bleeding[2].

Therapeutic alternatives for palliating DUB ranges from pharmacological treatments (hormonal and non-hormonal) to more aggressive surgical alternatives such as hysterectomy or endometrial ablation/resection. The levonorgestrel-releasing intrauterine system (LNG-IUS), marketed in Spain under the name of Mirena® for the treatment of idiopathic DUB, is a depot progestogen (non-surgical hormonal drug treatment) which guarantees a daily release of 20 µg of progestogen directly into the uterine cavity for at least five years[3]. Moreover, LNG-IUS is an alternative to the classic and surgical medical treatment for HMB and respects reproductive capacity[4]. In Spanish clinical practice, its greater effectiveness and high tolerability, have been demonstrated with regard to other non-surgical therapeutic alternatives[5-7]. Thus, the Spanish Society of Gynaecology and Obstetrics has recommended the use of LNG-IUS as first-line treatment for DUB, due to its multiple benefits[5]. However, it has not been evaluated the economic value of the treatment of DUB with LNG-IUS in Spain, yet.

The primary endpoint of this study was to determine the economic value of treatment for idiopathic DUB with the LNG-IUS versus other medical options in women who initially wish to preserve reproductive function in Spain.

MATERIALS AND METHODS

Model

A Markov Model of 6 months cycles was built to simulate resource use, symptom-free months (SFM), surgery-free months (SuFM) and quality of life (QoL) of a hypothetical cohort of women with idiopathic DUB treated with the most common therapy in Spain: (1) the levonorgestrel-releasing intrauterine system (LNG-IUS), (2) combined oral contraception (COC) and (3) progestogens (PROG) (figure 1). Tranexamic acid was excluded as a possible comparator as it is an acute treatment of the condition. The time horizon was established as 5 years, the LNG-IUS duration time, although, patients may continue with the same method by having a new device inserted after this period.

The model allows to calculate the costs per patient associated with each option and to estimate the incremental cost-effectiveness of first-line treatment with LNG-IUS versus the alternatives, compared by means of the following formula:

$$\frac{\text{Costs}_{\text{LNG-IUS}} - \text{Costs}_{\text{compared alternative}}}{\text{Effectiveness}_{\text{LNG-IUS}} - \text{Effectiveness}_{\text{compared alternative}}}$$

In addition, a cost-utility analysis was carried out, in which the clinical results were measured in quality-adjusted life months (QALM).

Due to the double indication of most of the treatments for DUB, four health states that combine the success/failure of the reduction of bleeding with success/failure in contraceptive control where defined. This allowed us to evaluate the specific results on bleeding reduction and those related to the interaction between both indications.

The study was designed from the perspective of the National Health System (NHS) and health-care decision-makers, including only direct health-care costs. Both future costs and effects where

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discounted at 3% as indicated by the Spanish guidelines[8] and we inflated all costs to 2008 € using the consumer price index for all goods and services[9].

Parameters of the model

The clinical and economic parameters of the model were extracted from the data published in the literature and validated by Spanish clinical experts (table 1). For progestogens, which are not a contraceptive treatment like the rest of the comparators, an 85% probability of contraception success was assumed, equivalent to the use of preservatives as the contraceptive method. On the other hand, a 100% efficacy and compliance for hysterectomy was assumed, thus rendering the possibility of treatment dropout impossible.

The transition of patients reflected in the model when some treatment no longer controls the DUB, as well as the proportion of women who, following a pregnancy/abortion with one of the treatments, switch treatment, were obtained by expert opinion by means of a *focus group* battery (figures 2-3). Similarly, due to the experts' comments, it was included in the model that 80% of the total surgical procedures are hysterectomies and 20% resections.

QALM constitutes an outcome measurement which includes the improvement in survival and gains in QoL. Utility values were obtained from data published according to the EuroQol-5D scale, where perfect health has a utility of 1, and the utility of death is 0. A utility of 0.95 was applied to DUB control, 0.55 to absence of DUB control, and 0.65 for patients undergoing surgery[16].

The use of health resources associated with each therapy was obtained from a group of Spanish clinical experts with experience in the management of these patients. Moreover, the pharmacological costs have been included in the model in Manufacturing Selling Price[17] weighted by market share when needed. It must be mentioned that the cost of COC was assumed to be zero in our model, since it is a cost that has to be taken on by the patient and falls beyond the health system perspective. For the rest of the costs, the Spanish health-costs Database eSalud[18] was used, which collects and updates Spanish costs from the literature and official tariffs from national

and regional health services[19]. The LNG-IUS cost included the device cost (Mirena®, 112 €), the introduction visit and an additional insertion in 5% of the patients due to spontaneous device expulsion[20] (table 2).

Sensitivity analysis

To evaluate the influence of the uncertainty of the parameters on results and to confirm the robustness of the outcomes obtained, a probabilistic sensitivity analysis was performed by means of a second-order Monte-Carlo simulation (1,000 times)[21]. For the sensitivity analysis, fixed distributions were selected (log-normal distribution for costs, normal distribution for resource use and beta distribution for probabilities) and the parameters of each distribution were estimated using the primary data collected[22].

Assumptions

It was assumed that all patients started a new treatment when a previous therapy failed to control DUB, following an algorithm representing usual clinical practice in Spain (figure 2). With regard to contraceptive control, if any of the therapies failed, two possibilities were taken into account: patients aborted or completed pregnancy. The assumptions of the model were to consider that 33% of the patients that get pregnant following contraceptive failure decide to abort (figure 3). In this case, they would not receive treatment for DUB again until 6-months after abortion. Sixty-seven percent of the women that decide to complete the pregnancy were assumed not to treat DUB until 12 months after delivery/childbirth.

RESULTS

Health outcomes

A review of the literature showed that control of DUB effectiveness after one year was achieved in 75% of patients with the LNG-IUS (efficacy 82%), in 36% of the patients with COC (efficacy 46%) and in 2% of the PROG group (efficacy 57%). Effectiveness of all options is strongly influenced by compliance rates, that are especially low in oral treatments such as COC or PROG, being only 4% in the PROG due to the number of associated complications. Six-months model outcomes showed that higher effectiveness of LNG-IUS translated to 5.21 SFM, 3.29 for COC and 1.32 for PROG. Therefore, patients with COC have suitable control of DUB for only 55% of the time after 6 months, a value which is less for patients on treatment with PROG (22% of the time) in comparison with LNG-IUS (87%) (table 3).

Patients starting treatment of DUB with LNG-IUS always presented a greater number of SFM for all time horizons (1st year 10.28 SFM and 5th year 50.53 SFM) and maintain DUB patients under control the 84-7% of the time (table 3).

The lower effectiveness of the treatment with COC and PROG leads to a rapid change of treatment, so that, at the end of the first simulated year, LNG-IUS contribuited a 19% and a 22% to the SFM of therapeutic lines initiated with COC and PROG, respectively (figure 4). This transfer to other treatments that takes place mainly in the therapeutic lines that start with COC or PROG leads to an improvement in the effectiveness of these therapeutic lines with regard to the effectiveness of the initial method, resulting, for COC and PROG, respectively, in 7.52 SFM and 5.13SFM in the first year and 47.86 SFM and 45.59 SFM after five years, still not achieving the levels of the therapeutic line of LNG-IUS (table 3).

Patient flow after five years showed that 20.7% patients were with LNG-IUS, 14.4% with resection, 64.1% with hysterectomy and 0.8% with the others treatments, if the patients were initially assigned to therapeutic lines as follow: LNG-IUS (20%), COC (40%) or PROG (20%).

It should be mentioned that the greater effectiveness of LNG-IUS means that patients, besides benefiting from a less aggressive treatment, presented a mean number of SuFM after five years of 34.79 months, while in patients in the therapeutic line starting with COC this figure was 30.31 months, and for patients of the therapeutic line starting with PROG it was 28.05 months. Thus, therapeutic lines beginning treatment with COC or with PROG are referred to surgery before that starting with LNG-IUS.

DUB considerably alters patients' daily activities, reflected in QoL (initially a reduction of 0.40 utility value respect to control state). In our study, QoL was greater for the therapeutic line starting with LNG-IUS than for the other alternatives (figure 5). The results indicated that QALM were 5.38 and 50.89, respectively, after 6 months and 5 years for the therapeutic lines starting with LNG-IUS, 4.61 and 49.82 with COC and 3.83 and 48.91 with PROG (table 3).

We also evaluated the scenario considering only DUB control without taking into account contraception and we observed similar values of SFM, SuFM and QALM for all the compared options (table 3).

Cost outcomes

Mean costs per patient were 586.17 €, 760.40 € and 816.71 € after 6 months, respectively, for the therapeutic lines initiated with LNG-IUS, COC and PROG. Hence, the treatment line starting with COC was associated to an increase in health-care costs per patient with regard to the therapy initiated with LNG-IUS of 174 € after 6 months of treatment and 310 € after five years. Treatment initiated with PROG increased health costs between 230 and 578 €. So, even taking into account the zero cost of COC for the NHS, the initial cost of implanting the LNG-IUS is offset in only 6 months. We can also see that the therapeutic line initiated with PROG always has the greater mean cost due to its limited rate of effectiveness (table 3).

Cost-effectiveness analysis

In view of the results obtained in the analysis for a 5-year time horizon, and including contraception control, the dominant therapeutic line was the one initiated with LNG-IUS, since it provided an

average cost per patient below the other therapies, providing with greater clinical benefits expressed as SFM, SuFM and QALM (figure 6).

If only the effectiveness of the different therapies for the control of DUB is taken into account, disregarding the success of contraceptive control, once again the therapeutic line initiated with LNG-IUS is a cost-saving option respect to all comparators, providing also greater clinical benefits, whereby once again it is the dominant treatment line. Comparatively, mean costs of all treatment alternatives increase, despite the fact that the cost of pregnancy was not considered in this scenario, probably due to earlier transfer to surgery.

Sensitivity analysis

In the univariate sensitivity analysis performed for the variables of the model that were regarded as most relevant, in all scenarios and for all timeframes, therapeutic line initiated with LNG-IUS proved to be dominant or cost-effective.

Robustness of results was tested considering the lowest efficacy value for LNG-IUS (74%) found by means of the literature review, showing the same results.

The results of the probabilistic analysis (1,000 different simulated patients) showed that taking into account the uncertainty in the main variables of the Markov Model, starting the treatment of DUB with LNG-IUS remains dominant versus the other alternatives. This indicates that even being a decision-maker's willingness to pay for the increment in quality-adjusted life months almost 0 €, the treatment of choice should still be LNG-IUS.

COMMENTS

The results of this study indicate that the option of initiating treatment for DUB with LNG-IUS, besides rendering it possible to preserve fertility, is associated to cost savings for the NHS as early as 6 months after treatment initiation and clearly provides a clinical and a QoL advantage for patients compared to using COC/PROG as first-line. Also, patient flow at five years from treatment initiation with LNG-IUS, COC or PROG shows that patients remain using LNG-IUS or have undergone surgery.

It is important to remark that the cost-utility analysis performed took utility values published by a work by Sculpher[16] which, on the date of this analysis, was the only work from which this type of figures could be obtained. The values of the study in question present important limitations. On the one hand, they were obtained using a technique known as Time Trade Off in a sample of 60 women with complication-free DUB in the UK. The assigned value to the health state of the women with DUB was 0.55, a value which in principle seems very low, since according to this technique this value suggests that women would exchange almost 50% of their future life expectancy to avoid this health status. Moreover, they assigned a utility value of 0.95 for the non-DUB health status, which, taking into account that by convention the value of 1 is perfect health, indicates that the impact of the HMB in women of the sample was very significant. However, most of the international economic studies have used these utilities.

To date, this is the first economic evaluation of LNG-IUS in the Spanish setting. The international literature contains some similar studies which compare the different surgical techniques[23-24], and some included LNG-IUS[25-29], although none of the studies may be directly comparable to this one. The only studies that have used a mathematical simulation model similar to the one built for the Spanish setting in this analysis are those by You et al., Clegg et al. and Blumenthal et al.[25,28-29].

In the study by You et al.[29], which built a Markov Model and evaluated LNG-IUS, resection, hysterectomy and oral medication to a time frame of 5 years from the perspective of the NHS of Hong Kong. Results were expressed as cost-utility ratios, handling the same utility values we used

in our studies[16]. In that case, results were very similar to our owns, showing that treatment with LNG-IUS was dominant; however, they only took into account treatment effectiveness in the control of DUB without addressing the contraceptive issue.

The study by Clegg et al.[28] also built a Markov Model, and evaluated LNG-IUS, resection and hysterectomy over a timeframe of 5 years, from the perspective of the English National Health Service. The results of this analysis were in the same line as those obtained in our work, showing that patients beginning therapy with LNG-IUS presented lower costs and greater QALM than the other alternatives.

On the other hand, the work by Blumenthal et al.[25] is the closest to ours, since it is a Markov Model with a timeframe of 5 years, comparing combined oral contraception, LNG-IUS, resection and hysterectomy. Moreover, the patients' contraception intent is taken into account, and therefore included the possibility of contraceptive failure of the therapy in the analysis. The results were expressed as cost per success in DUB control and showed that treatment with LNG-IUS was the most cost-effective option.

It is worth to remark that the assumptions made to palliate the limitations of our model were conservative. Despite all this, in all scenarios in which this therapy was addressed the initial cost of the implantation of LNG-IUS is offset thanks to its higher effectiveness in the control of DUB, making that only a small proportion of patients need to undergo surgery, which is ultimately more aggressive and costlier.

In conclusion, the economic evaluation of beginning the treatment for DUB with LNG-IUS versus beginning with other options compared in this study indicates that LNG-IUS should be the non-surgical treatment of choice for the control of dysfunctional uterine bleeding, as it is more effective and less costly for the health system in Spain.

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REFERENCES

1. Matorras R, Ocerin I. Menorragia : Estado actual de los conocimientos. Folia Ginecológica 2000;25:9-31.

2. Comino R. Hemorragia uterina disfuncional. Introducción. In Comino R "Hemorragia uterina disfuncional". Barcelona, Prodinsa S.A.,1993,pp:11-18.

3. Spanish Ministry of Health and Consumer Affairs: Spanish Drug Agency. Product Information. Mirena®. 2008. [Cited on: July 20, 2008] Available at: http://www.agemed.es/en/home.htm

4. Marjoribanks J, Lethaby A, Farquhar C. Tratamiento quirúrgico versus tratamiento médico para el sangrado menstrual abundante (Translated Cochrane Revision). In: The Cochrane Plus Library, 2007 Issue 4. Oxford: Update Software Ltd. [Cited on: July 20, 2008] Available at: http://www.update-software.com. (Translated from The Cochrane Library, 2007 Issue 4. Chichester, UK: John Wiley & Sons, Ltd.).

5. Lete I, Obispo C, Izaguirre F, Orte T, Rivero B, Cornellana MJ, et al. The levonorgestrel intrauterine system (Mirena®) for treatment of idiopathic menorrhagia. Assessment of quality of life and satisfaction. The European Journal of Contraception & Reproductive Health Care 2008;13(3):231–237.

6. Alcázar M, Martínez C, Mattos I, Ripollés M, De Miguel S, Lorenzo A, et al. Sistema intrauterino de liberación de levonorgestrel (Mirena®). Seguimiento a largo plazo. 7th Congress of the SEC. 2004 [Cited on: July 20, 2008] Available at: http://www.sec.es/area_cientifica/ponencias_comunicaciones_congresos_sec/2004_07Co ngresoSEC/PDFcomunicaciones/O007%20Sistema%20intrauterino%20de%20liberacion% 20de%20levonogestrel.pdf

7. Núñez MT, Carbajo ML, Valdés J, Velázquez P. How do users rate the levonorgestrel intrauterine device? IX Congress of the SEC, Seville 2008.

8. López Bastida J, Oliva J, Antoñanzas F, García-Altés A, Gisbert R, Mar J, et al. Propuesta de guía para la evaluación económica aplicada a las tecnologías sanitarias. Madrid: National Plan for the NHS of the MSC. Evaluation Service of the Canary Islands Health Service; 2008. Health Technology Assessment Report: SESCS No. 2006/22

9. INE (National Statistics Institute). Consumer Price Index. 2008 [Cited on: July 20, 2008]. Available at http://www.ine.es

10. Fraser IS, McCarron G. Randomized trial of 2 hormonal and 2 prostaglandin-inhibiting agents in women with a complaint of menorrhagia. Aust N Z J Obstet Gynaecol 1991;31:66–70.

11. Irvine GA, Campbelle-Brown MB, Lumsden MA, Heikkilä A, Walker JJ, Cameron IT. Randomised comparative trial of the levonorgestrel intrauterine system and nore thisterone for the treatment of idiopathic menorraghia. Br J Obstet Gynaecol 1998;104:492-8.

12. Crosignani PG, Vercellini P, Apolone G, De Giorgi O, Cortesi I, Meschia M. Endometrial resection versus vaginal hysterectomy for menorrhagia: Long-term clinical and quality-of-life outcomes. Am J Obstet Gynecol 1997;177:95–101.

13. Istre O, Trolle B. Treatment of menorrhagia with the levonorgestrel intrauterine system versus endometrial resection. Fertility and Sterility 2001;76:304-9.

14. Torrejon R, Cayuela E, Comino R, Gilabert J, Hernández JJ, Labastida R, et al. Ablación endometrial. SEGO Consensus Documents. Meditex eds.Madrid. 2001:49-82.

15. Lethaby A, Shepperd S, Cooke I, Farquhar C. Endometrial resection and ablation versus hysterectomy for heavy menstrual bleeding. Cochrane Database Syst Rev 2000;(2):CD000329. Review

16. Sculpher M. A cost–utility analysis of abdominal hysterectomy versus transcervical endometrial resection for the surgical treatment of menorrhagia. Int J Technol Assess Health Care 1998;14:302–19.

17. Medicine database of medicines of the General Council of Official Associations of Pharmacists. [On line] [Cited on: July 20, 2008]. Available at: http://www.portalfarma.com

18. e-Salud health costs database. [On line] [Cited on: July 20, 2008]. Available at: http://www.oblikue.com

19. Ministry of Health and Consumer Affairs. Related Diagnostic Groups. 2005. [Cited on: July 20, 2008]. Available at http://www.msc.es

20. Stewart A, Cummins C, Gold L, Jordan R, Phillips W. The effectiveness of the levonorgestrel-intrauterine system in menorrhagia:a systematic review. Br J Obstet Gynaecol 2001;108:74-86.

21. Briggs AH. Handling uncertainty in cost-effectiveness models. Pharmacoeconomics 2000; 17 (5): 479-500.

22. Claxton K, Schupher M, McCabe C, Briggs A, Akehurst R, Buxton M, et al. Probabilistic sensitivity analysis for NICE technology assessment: not an optional extra. Health Econ 2005; 14: 339-47.

23. Garside R, Stein K, Wyatt K, Round A, Pitt M. A cost–utility analysis of microwave and thermal balloon endometrial ablation techniques for the treatment of heavy menstrual bleeding. BJOG 2004;111:1103–14.

24. Garside R, Stein K, Wyatt K, Round A, Price A. The effectiveness and cost-effectiveness of microwave and thermal balloon endometrial ablation for heavy menstrual bleeding: a systematic review and economic modeling. Health Technol Assess 2004;8:iii,1–15.

25. Blumenthal PD, Trussell J, Singh RH, Guo A, Borenstein J, Dubois RW, et al. Cost-effectiveness of treatments for dysfunctional uterine bleeding in women who need contraception. Contraception 2006;74:249-58.

26. Brown PM, Farquhar CM, Lethaby A, Sadler LC, Johnson NP. Cost-effectiveness analysis of levonorgestrel intrauterine system and thermal balloon ablation for heavy menstrual bleeding. BJOG. 2006;113:797-803.

27. Hurskainen R, Teperi J, Rissanen P, Aalto AM, Grenman S, Kivelä A, et al. Quality of life and costeffectiveness of levonorgestrel-releasing intrauterine system versus hysterectomy for treatment of menorrhagia: a randomised trial. Lancet. 2001;357:273-7.

28. Clegg JP, Guest JF, Hurskainen R. Cost-utility of levonorgestrel intrauterine system compared with hysterectomy and second generation endometrial ablative techniques in managing patients with menorrhagia in the UK. Curr Med Res Opin 2007;23:1637-4.

29. You JH, Sahota DS, MoYuen P. A cost-utility analysis of hysterectomy, endometrial resection and ablation and medical therapy for menorrhagia. Hum Reprod 2006;21:1878-83.

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Ethics approval declaration: Not-required

Table 1. Rate of effectiveness after one year

     *It is assumed to be the same as for preservatives.

Table 2: Unit costs

     *Cost of the device plus one visit and additional reinsertion in 5% of the patients

Table 3: Results of the cost-effectiveness and cost-utility analysis

     -

Figure 1: Markov Model

     State **SS**: Success in the reduction of DUB and success in contraceptive control.

     Status **SF**: Success in the reduction of DUB and failure in contraceptive control.

     State **FS**: Failure in the reduction of DUB and success in contraceptive control.

     State **FF**: Failure in the reduction of DUB and failure in contraceptive control.

     COC= Combined oral contraception; PROG= Progestogens; LNG-IUS = Levonorgestrel-releasing intrauterine system

Figure 2: Treatment cascade in case of treatment failure in DUB control

     COC= Combination oral contraceptivon; PROG= Progestogens; LNG-IUS = Levonorgestrel-releasing intrauterine system

     * It is assumed that 20% of the patients undergo resection and 80% hysterectomy

Figure 3: Failure in contraceptive control

     COC= Combination oral contraception; PROG= Progestogens; LNG-IUS = Levonorgestrel-releasing intrauterine system

Figure 4. Relative contribution of the therapeutic alternatives to effectiveness (SFM)

     COC= Combined oral contraception; PROG= Progestogens; LNG-IUD = Levonorgestrel-releasing intrauterine system

Figure 5: Increase in quality of life (%) of LNG-IUS versus the comparators in different time frames

     COC= Combined oral contraception; PROG= Progestogens

Figure 6. Cost-effectiveness plane

     -

Table

Table 1. Rate of effectiveness after one year

Therapy	Dysfunctional Uterine Bleeding Control	Contraceptive control	References
LNG-IUS	75%	99.9%	5
Combination oral contraceptives	36%	92%	10
Progestogens	2%	85%*	11
Resection	94%	100%	12-14
Hysterectomy	100%	100%	15

Table 2: Unit costs

Resource	Unit cost (€, 2008)	References
LNG-IUS*	159.43 €	17-18
Combination oral contraceptives	0	17
Progestogens	12.72	17
Resection	2,117 €	18
Hysterectomy	4,234 €	18
Gynaecology visit (First visit)	78.9 €	18
Gynaecology visit (successive visits)	39.45 €	18
Abortion	1140.41 €	18
Partum	2,000 €	19

Table 3: Results of the cost-effectiveness and cost-utility analysis

|			6 MONTHS			1 YEAR			5 YEARS		
			LNG-IUS	COC	PROG	LNG-IUS	COC	PROG	LNG-IUS	COC	PROG
DUB/Contraception	COST		586.17 €	760.37 €	816.71 €	987.64 €	1,323.41 €	1,529.98 €	3,099.37 €	3,409.32 €	3,676.98 €
		Difference	-	-174.20 €	-230.54 €	-	-335.77 €	-542.34 €	-	-309.95 €	-577.61 €
	SFM		5.21	3.29	1.32	10.28	7.52	5.13	50.53	47.86	45.59
		Difference	-	1.92	3.89	-	2.75	5.14	-	2.67	4.94
	Cost/ SFM gained		**-**	**Dominant**	**Dominant**	**-**	**Dominant**	**Dominant**	**-**	**Dominant**	**Dominant**
	SuFM		6	6	6	11.25	10.81	10.78	34.79	30.31	28.05
		Difference	-	0.00	0.00	-	0.43	0.47	-	4.47	6.74
	Cost/ SuFM gained		**-**	**Dominant**	**Dominant**		**Dominant**	**Dominant**	**-**	**Dominant**	**Dominant**
	QALM		5.38	4.61	3.83	10.62	9.51	8.56	50.89	49.82	48.91
		Difference	-	0.77	1.56	-	1.10	2.06	-	1.07	1.98
	Cost/ QALM gained		**-**	**Dominant**	**Dominant**	**-**	**Dominant**	**Dominant**	**-**	**Dominant**	**Dominant**
			6 MONTHS			1 YEAR			5 YEARS		
DUB	COST		625.81 €	799.82 €	841.97 €	1,027.10 €	1,347.91 €	1,526.98 €	3,137.33 €	3,328.93 €	3,545.09 €
		Difference	-	-174.01 €	-216.16 €	-	-320.81 €	-499.88 €	-	-191.60 €	-407.76 €
	SFM		5.21	3.40	1.68	10.28	7.59	5.28	50.52	47.70	45.30
		Difference	-	1.81	3.52	-	2.69	5.00	-	2.82	5.22
	Cost/ MLS gained		**-**	**Dominant**	**Dominant**	**-**	**Dominant**	**Dominant**	**-**	**Dominant**	**Dominant**
	SuFM		6.00	6.00	6.00	11.25	10.81	10.78	34.65	29.93	27.04
		Difference	-	0.00	0.00	-	0.43	0.47	-	4.72	7.61
	Cost/ SuFM gained		**-**	**Dominant**	**Dominant**	**-**	**Dominant**	**Dominant**	**-**	**Dominant**	**Dominant**
	QALM		5.38	4.66	3.97	10.62	9.54	8.62	50.89	49.76	48.80
		Difference	-	0.72	1.41	-	1.08	2.00	-	1.13	2.09
	Cost/ QALM gained		**-**	**Dominant**	**Dominant**	**-**	**Dominant**	**Dominant**	**-**	**Dominant**	**Dominant**

Figure1

Figure 1: Markov Model
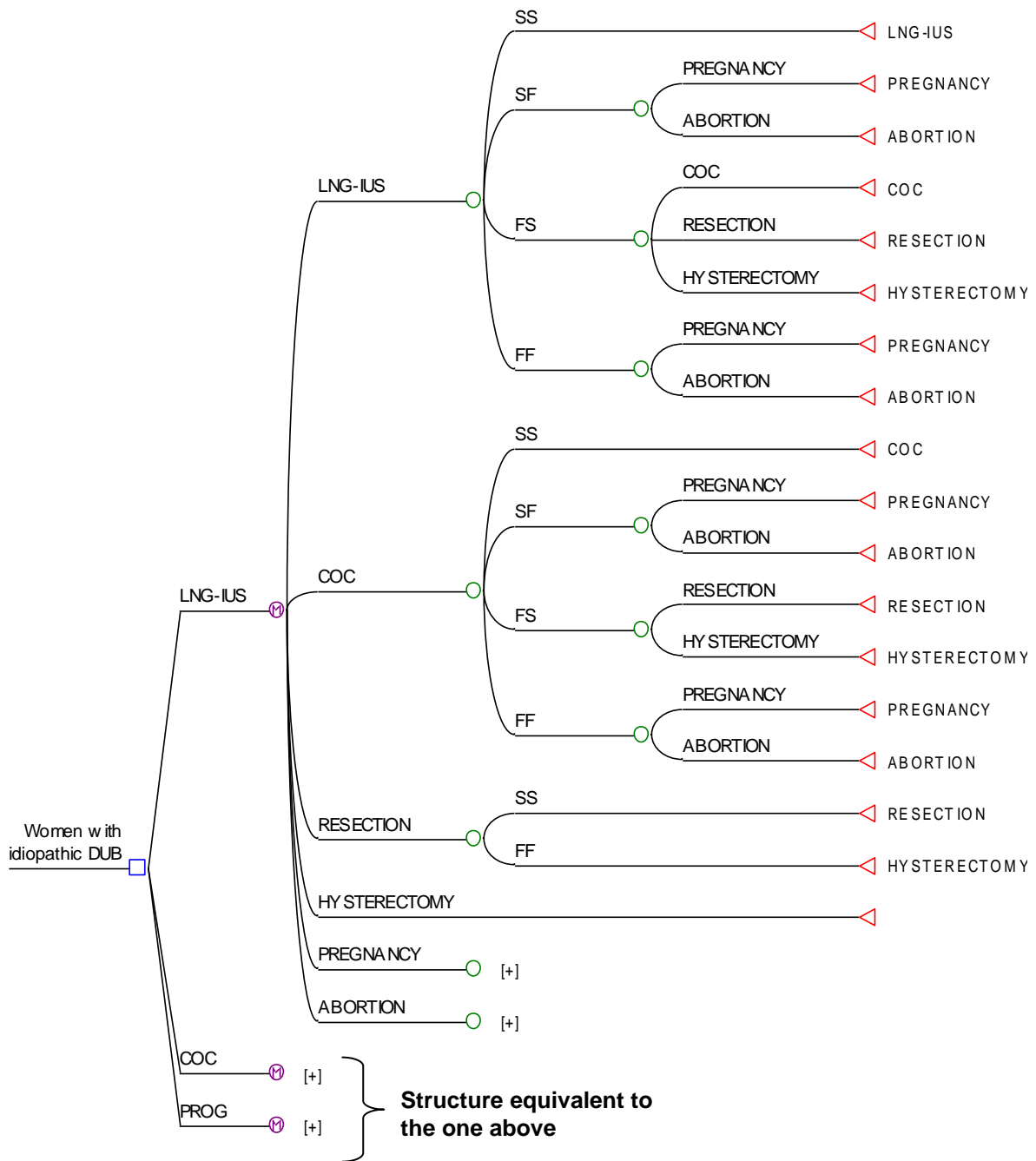
Figure2

Figure 2: Treatment cascade in case of treatment failure in DUB control
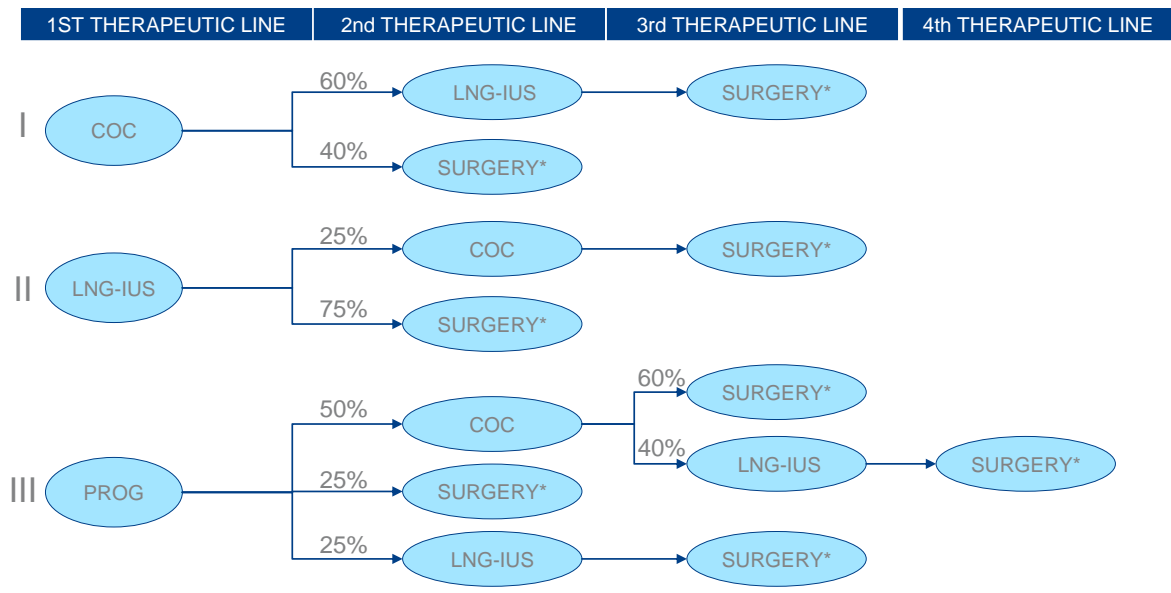
Figure3

Figure 3: Failure in contraceptive control
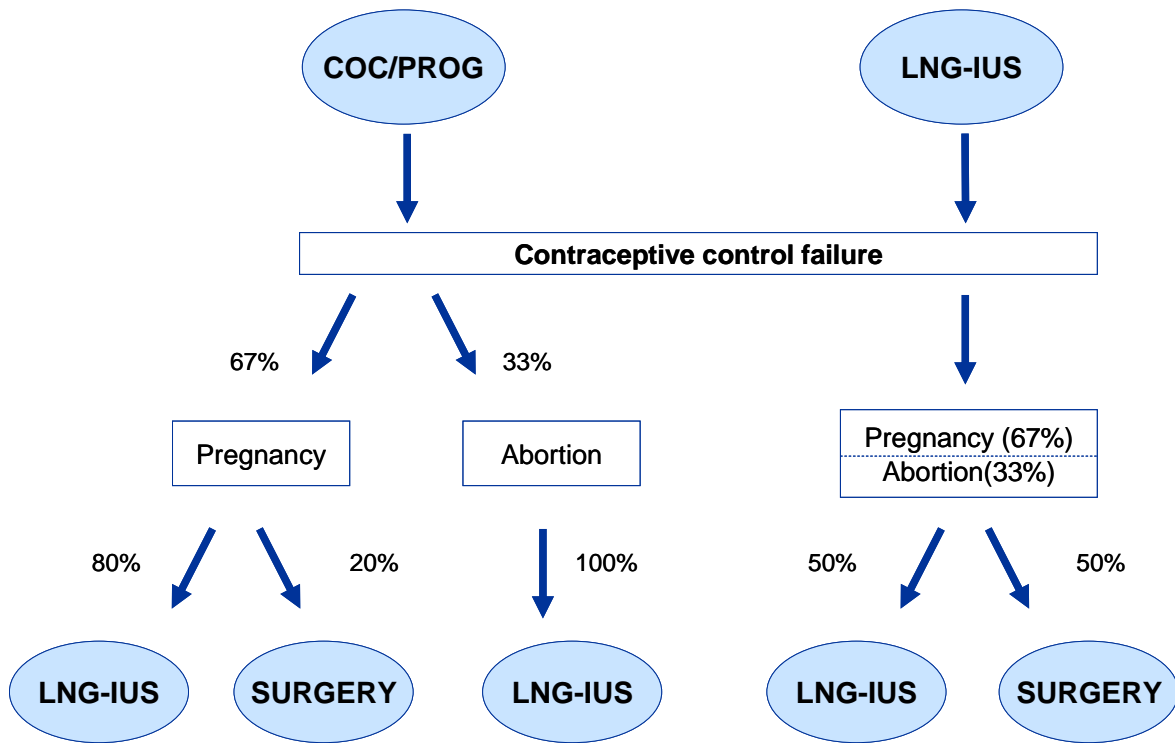
Figure4

Figure 4. Relative contribution of the therapeutic alternatives to effectiveness (SFM)
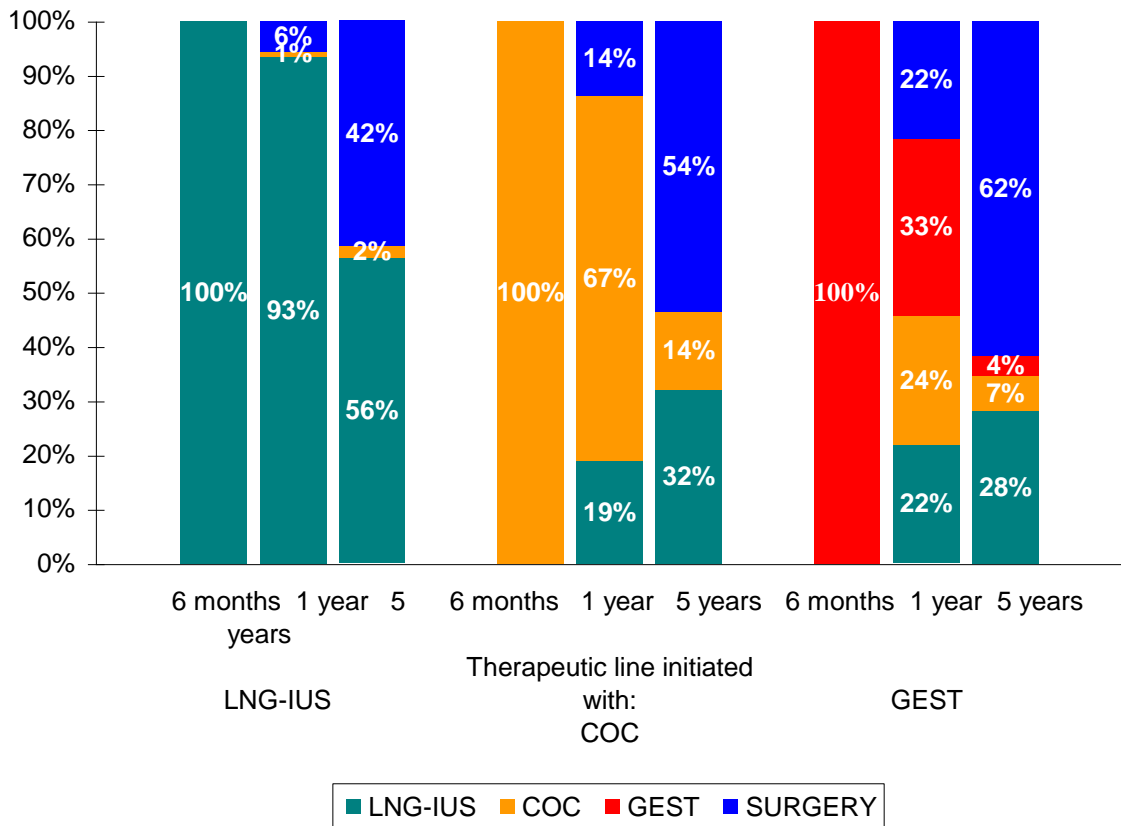
Figure5

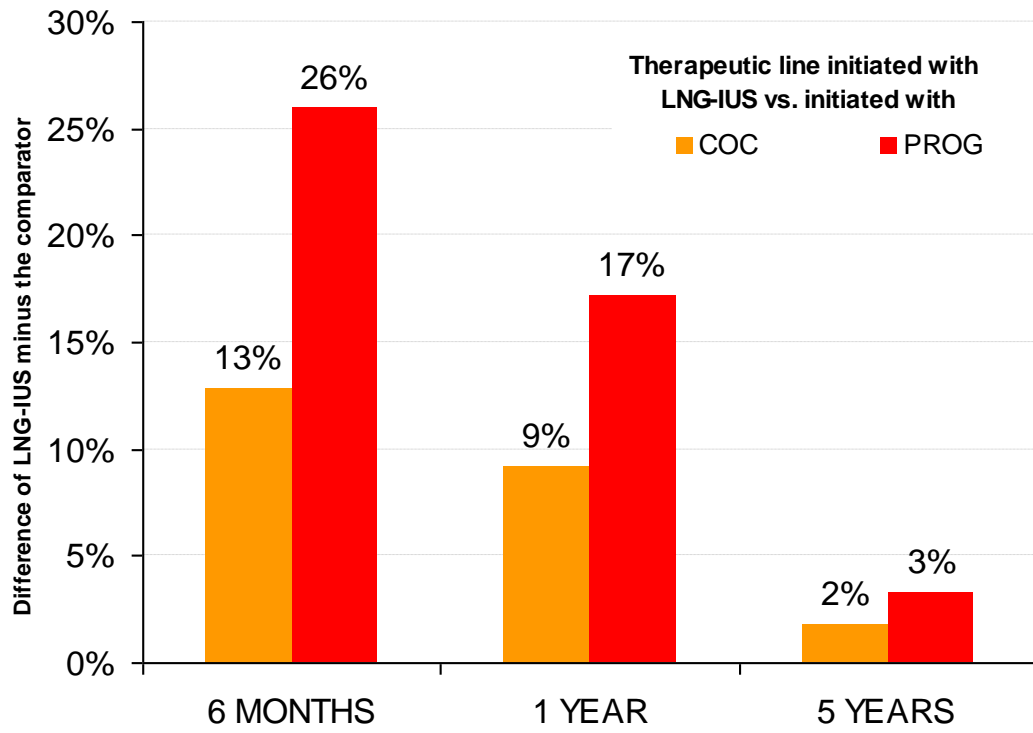Figure 5: Increase in quality of life (%) of LNG-IUS versus the comparators in different time frames

Figure6

Figure 6. Cost-effectiveness plane