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DE DOCTEUR EN MÉDECINE

Evaluation de l'association de Mifepristone et Misoprostol en comparaison du Misoprostol seul dans la prise en charge médicamenteuse des fausses couches précoces : une étude coût efficacité.

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AVERTISSEMENT

La Faculté n'entend donner aucune approbation aux opinions émises dans les thèses : celles-ci sont propres à leurs auteurs.

TABLES DES MATIÈRES

LISTE DES ABRÉVIATIONS

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CCAM classification commune des actes médicaux

ENC études nationales de coûts

EPL early pregnancy loss

GHM groupe homogène de malade

ICER incremental cost-effectiveness ratio

MF mifepristone

MS misoprostol

PO per os

PV per vagina

RCT randomized control trial

SE surgical evacuation

UK United Kingdom

US ultrasound

USA United States of America

ABSTRACT

Objective – Early pregnancy loss (EPL) is the first pregnancy complication affecting 25% women, resulting in substantial health care costs. This work intended to evaluate the cost effectiveness of two strategies in the medical management of EPL in France: Mifepristone + Misoprostol (MF+MS) VS Misoprostol (MS) alone.

Methods – A decision tree model was constructed to compare these two strategies. The strategy under evaluation was the protocol applied in Lille, France. Data were extracted from five studies (RCT and crossover prospective study) issued of a systematic literature review conducted from 2000 to 2021. The primary outcome was gestational sac expulsion without surgical evacuation. The result was expressed as the incremental cost-effectiveness ratio (ICER). Determinist and probabilistic sensitivity analysis were performed to evaluate uncertainty.

Results –1334 women were considered 657 treated with MF+MS and 677 with MS alone. The effectiveness of MF+MS is superior to MS alone 79%(IC 95% 0,76 - 0,81) VS 68%(IC 95% 0,65 - 0,71) with lower costs 953.01€ (IC 95% 712,34 à 1273,32€) VS 1238,30€ (IC 95% 866,63 à 1721,28€). The ICER is calculated as the ratio -2557.86€ meaning that MF+MS strictly dominates MS alone. This conclusion is consistent with deterministic and probabilistic sensitivity analysis: ICER -2557.96€ (95% CI: [-2613.66 ; -2461.56€]).

Conclusion – MF+MS is a most cost effectiveness strategy than MS alone for the medical management of EPL from a French healthcare perspective.

KEYWORDS : cost effectiveness, early pregnancy loss, mifepristone pretreatment, mifepristone association, medical management, surgical evacuation

INTRODUCTION

Au cours de leur vie, une fausse couche survient chez un quart des femmes (1). D'après Quenby et al. en 2021 (2), cette complication surviendrait dans 15,3% des grossesses.

Bien que la plupart des fausses couches précoces s'expulsent spontanément, une intervention médicale peut s'avérer nécessaire. Pendant des années, le curetage chirurgical a été le traitement de référence ; cependant, aujourd'hui, le traitement médical est devenu une alternative sûre et efficace. La plupart des communautés scientifiques recommandent l'utilisation du Misoprostol (MS). En France, depuis les dernières recommandations de 2014, deux stratégies sont proposées aux femmes ayant un diagnostic de fausse couche précoce, le traitement médical avec le MS seul ou le traitement chirurgical par le biais d'un curetage. L'attitude expectative n'est plus proposée car elle diminue l'efficacité du traitement médical et augmente le risque d'endométrite et de saignement abondant.

Si l'intérêt de l'ajout de la Mifépristone (MF) n'est plus à démontrer dans la prise en charge de l'interruption (volontaire ou médicale) de grossesse ou de la mort fœtale in utero (3), son utilisation en cas de fausse couche précoce est toujours en évaluation. En effet, en 2018, Schreiber et al. ont constaté que l'association MF+MS conduisait à 83,8% d'expulsion du sac gestationnel sans recours au curetage contre 67,1% avec MS seule (OR = 1,20 IC95%, 1,09 à 1,43) (4). En 2020, Chu et al. ont également démontré que la prise de MF entrainait moins de curetage que chez les femmes traitées par MS seul (5).

Considérant un tel problème de santé publique, il apparaît essentiel de proposer une stratégie sûre et efficace aux femmes qui choisissent un traitement médical afin d'éviter un curetage. Le coût de cette stratégie ne peut toutefois pas être ignoré. Selon

Quenby et al, 526 millions d'euros (421 millions de livres sterling) sont dépensés chaque année au Royaume-Uni (2) pour la prise en charge des fausses couches précoces. D'un point de vue économique, il semble important de comparer l'efficacité et le coût des stratégies concurrentes.

L'objectif de cette étude est d'évaluer le rapport coût-efficacité de l'association MF + MS versus MS seul dans la prise en charge des fausses couches avant 14 semaines d'aménorrhées chez les femmes qui choisissent un traitement médical.

INTRODUCTION

During their life, one-fourth of women experience an early pregnancy loss (EPL) (1), which corresponds to 15.3% of all pregnancies according to Quenby et al. in 2021 (2). Most of EPL end in spontaneous miscarriage but a clinical intervention could be necessary. Although surgical evacuation (SE) was the reference for years, medical treatment has become a safe and effective alternative. Nowadays, most of scientific communities recommend medical management using Misoprostol (MS). In France, since the last recommendations of 2014, two strategies are proposed to women with a diagnosis of EPL, medical treatment with MS alone or surgical treatment with a surgical evacuation (curettage). The expectant strategy is no longer proposed because it leads to more infection and important bleeding. If the interest of the addition of Mifepristone (MF) is no longer in doubt in the management of abortion, in utero fetal death or termination of pregnancy (3), its use in case of EPL is still under evaluation. Indeed, in 2018, Schreiber et al. found that MF+MS lead to 83.8% of gestational sac expulsion without recourse of surgical evacuation compared with 67.1% for MS alone (OR = 1.20 CI95%, 1.09 to 1.43) (4). In 2020, Chu et al. also demonstrated that women pre-treated with MF required less SE than women treated with MS alone (5).

It is essential to propose a safe and effective strategy to women who choose medical treatment to avoid a surgical evacuation and cost cannot be ignored. According to Quenby and al., 526 million euros (£421 million) are spent each year on the management of EPL in the UK (2). From an economic perspective, it seems important to compare effectiveness and cost of the competing strategies.

The objective of this study is to evaluate the cost-effectiveness of the association MF + MS versus MS alone for the management of EPL before 14 weeks of gestation for women who choose a medical treatment.

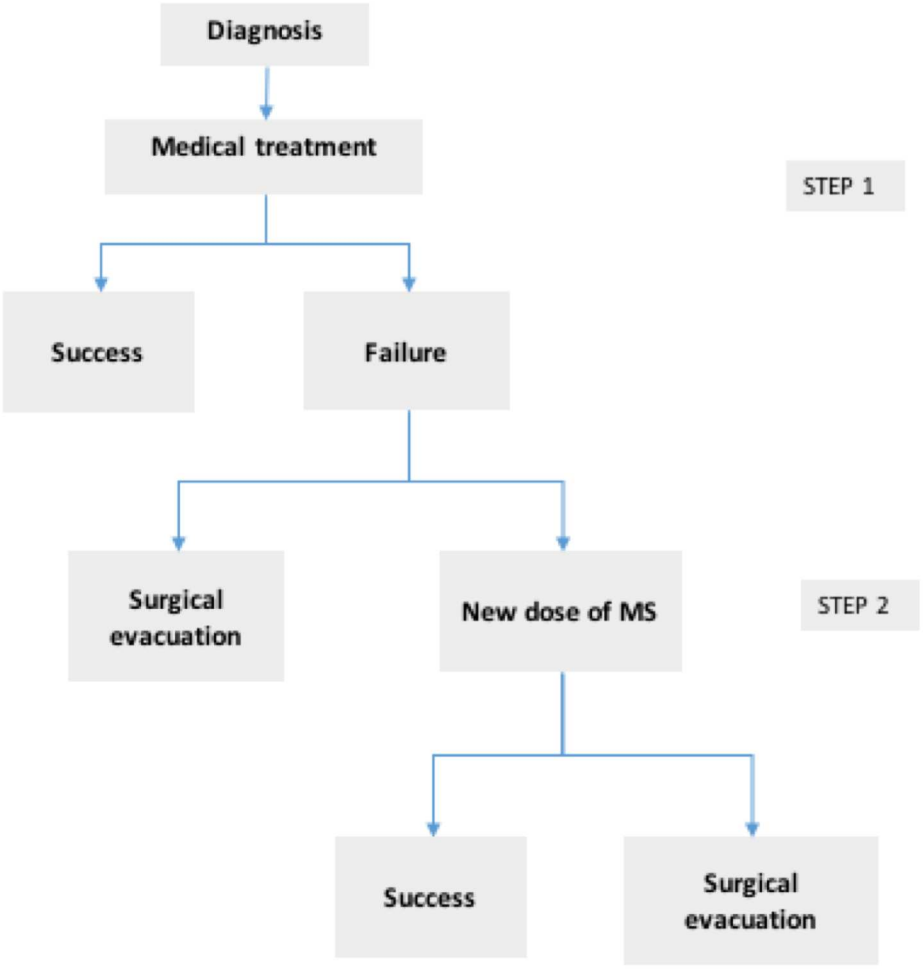
METHODS

Management of early pregnancy loss

Our analysis focuses on women experiencing an EPL. We consider EPL as fetal demise or embryonic and anembryonic gestation before 14 weeks of pregnancy. Incomplete miscarriages are excluded (4–8). The diagnosis is performed after gynecologic exam and pelvic ultrasound scan, at the emergency department. After diagnosis, two managements are possible: medical treatment or SE. This study only focuses on women who choose the medical treatment in first-line according to their own preferences (9).

The strategy under evaluation is the medical protocol applied in the department of gynecologic emergencies of our center (Lille, France, 24000 consultations per year). Two medical strategies are compared: pretreatment with Mifepristone (MF + MS) and Misoprostol alone (MS alone) which is the reference strategy (**Figure 1)**.

Figure 1. Diagram of the medical protocol use in the model



Success : gestationnal sac expulsion

The care pathway of the protocol is as follows:

> **MF + MS**: a dose of 200mg of MF is taken orally at the hospital. Twenty-four hours later, one to three doses (depending on bleeding intensity) of MS (400µg) are taken orally at home. After 7-10 days an ultrasound checking is realized. This visit could be performed earlier (after 48 hours) if no bleeding occurred after 3 doses of MS. A successful treatment is considered if the endometrial thickness is less than 15mm. In case of failure, woman has the choice between new doses of MS (one to three of 400µg) or SE. After this new dose, ultrasound evaluation is performed 7-10 days after. If the endometrial thickness is still over 15mm a SE is performed.

> **MS alone**: one to three doses (depending on bleeding intensity) of MS (400µg) is taken orally at home the same day of the diagnosis. Then, the same protocol as with MF+MS is followed.

The primary outcome was gestational sac expulsion, as defined above, without recourse of surgical evacuation within 30 days after medical treatment. In this study, surgical evacuation was considered as failure, anytime it would happen during the protocol since this end is not aligned with women's initial preferences. The time horizon was 30 days corresponding to time between the first and the last consultation; minimum three days, maximum thirty days. The analysis was performed from a healthcare payer perspective.

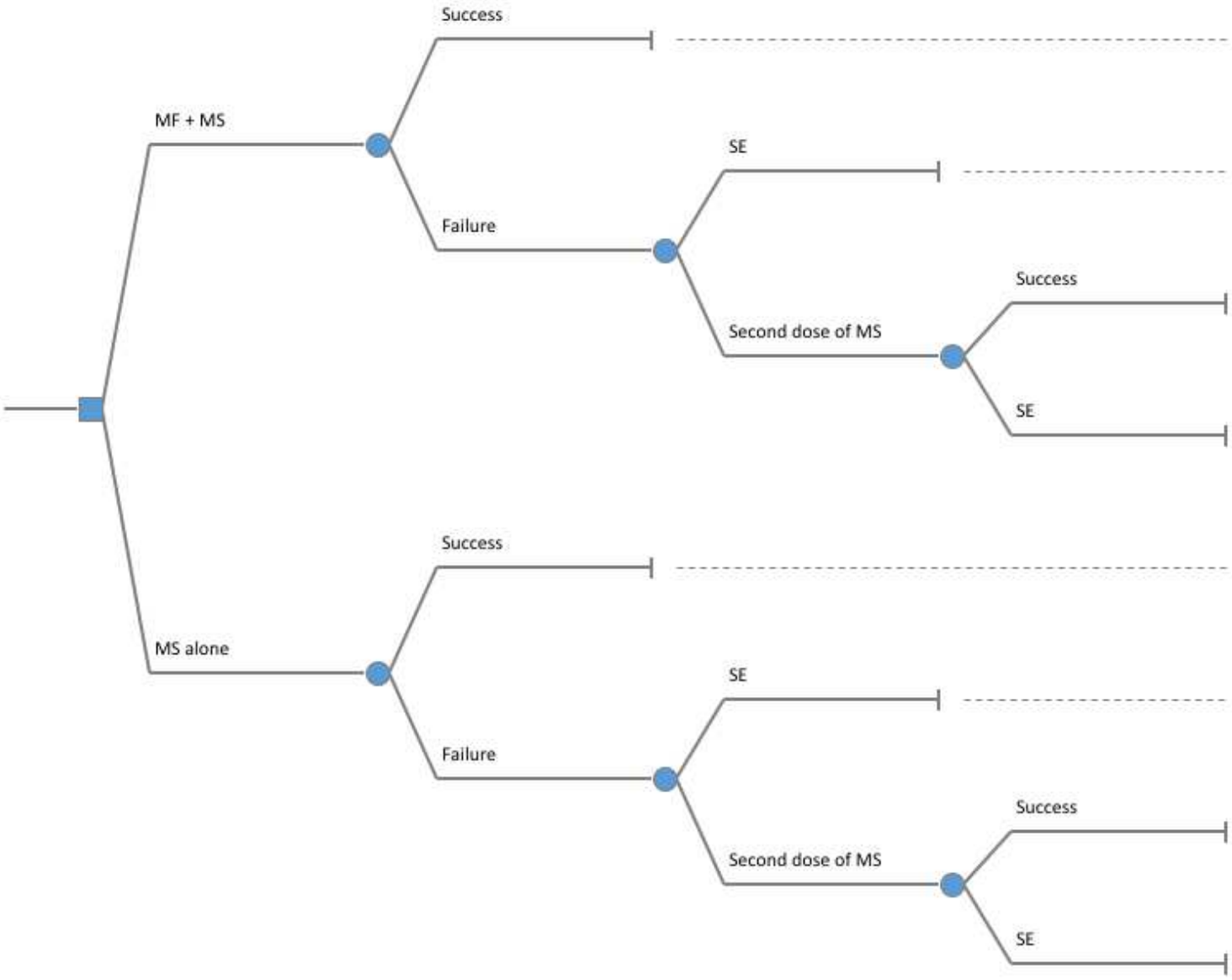
Model structure

A decision tree is the simplest decision-making model. It describes the successive medical management phases for a representative patient. The branches of the tree trace events (chance nodes, represented as circles) or decisions (decision nodes, represented as squares) occurring/taken during the follow-up. At each chance node, the probabilities sum to one. Terminal pay-off values are computed by summing costs and/or utilities along each branch. The tree is then rolling back to determine the expected effectiveness and the expected cost associated to evaluated strategies.

Construction of the model used the software Treeplan^{TM} for Excel 2016 (Decision Toolworks, San Francisco – Microsoft Corporation, USA) (**Figure 2)**.

We chose a decision tree because EPL is a short and acute event, and complications are well-known and documented.

Figure 2. Decision Tree Model



Model input parameters

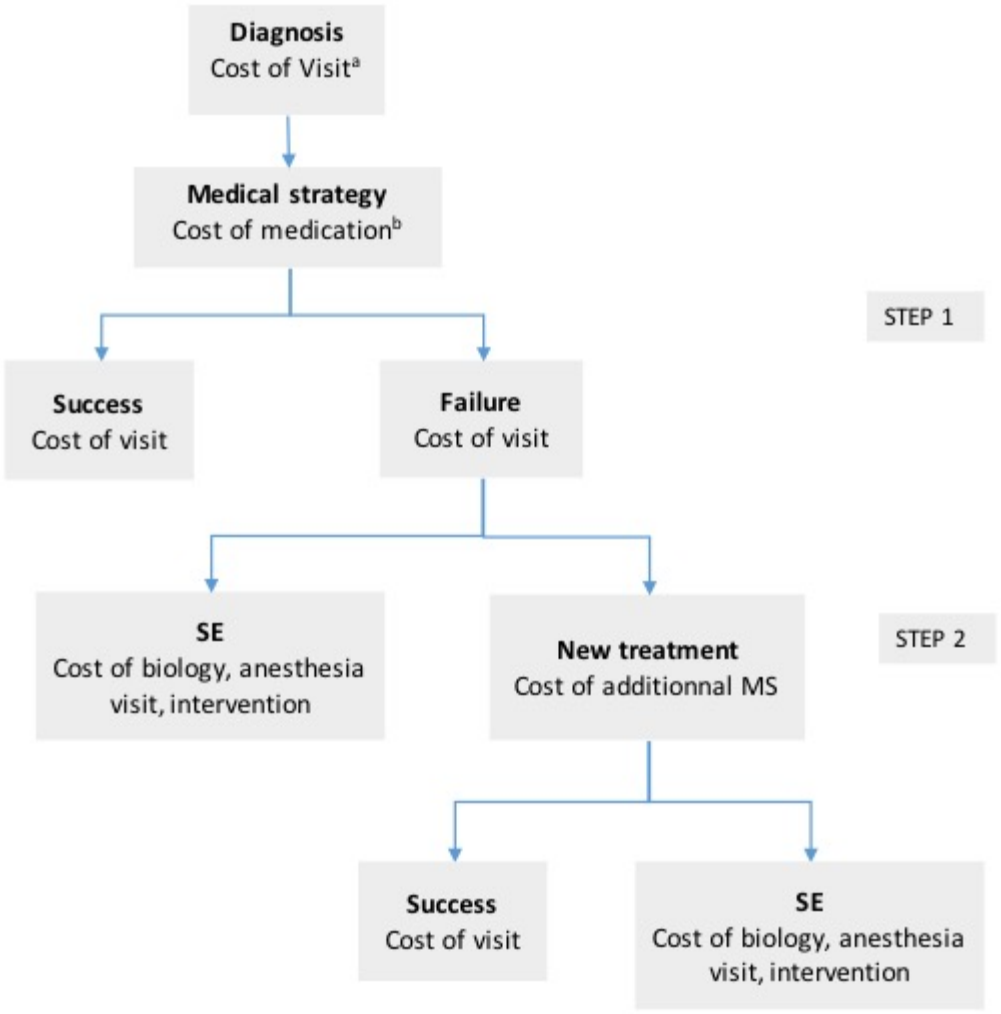
Data were extracted after a systematic literature review. This review was performed with a computerized PubMed and Cochrane search of articles published between January 2000 and January 2021 to identify all studies comparing MF + MS with MS alone in the management of EPL. Following key words were search: “early pregnancy failure or loss” or “miscarriage” and “medical management” or “mifepristone” and “misoprostol” or “combined treatment”. References or retrieved articles were also analyzed. All articles related to abortion were excluded. Only studies with high level of

proof (RCT and prospective study) were considered. All data were extracted by one author (A.B) and checked by two others (C.G and B.D). Authors were contacted for getting additional data when non available in published supports.

Estimates of effectiveness. Effectiveness data were extracted from published study selected. For each study, number of success and failure was noted using the medical protocol describes in **Figure 1**. To ensure the accuracy of the results we had to recalculate data from studies which had a different protocol from ours. It was only data concerning the number of patients included. In particular, we excluded data related to a first surgical treatment or an expectant attitude. Once these data extracted they were pooled together.

Estimates of costs. Costs data were obtained from different sources. All costs are presented in 2020€. Costs are considered at each step of the protocol as described in the flow diagram in **Figure 3**. Regarding the short time horizon (30 days), costs are not discounted.

Figure 3. Flow diagram for costs



a: cost of visit: consultation + US
b: MF + MS or MS alone

The cost of a visit, including a consultation and an ultrasound, was obtained after analyzing data of a three-month period at the emergencies of Lille University Hospital (n=28). Medical professional (resident or senior), moment (day or night) and day (week or Sunday) of the visit was considered because it could impact costing. This analyzing gave the distribution, mean and standard error of the cost of a visit.

The cost of medication was obtained from data provided by the Lille University Hospital's pharmacy. For the MF the cost was fixed since only one dose was given. For the cost of MS, since one to three doses could be taken, a varied cost was

calculated. Using the data from the selected studies, we calculated the number of women who took one, two or three doses of MS, thus allowing to estimate the distribution, mean and standard error of the cost of MS.

The cost of the hospital stay for SE was estimated from the French National Costs Study (ENC) between 2010 and 2016 using the act related group “Evacuation of a pregnant uterus by aspiration and/or curettage in the 1st trimester of pregnancy” (code CCAM JNJD002). Among this group several diagnostics are possible, we selected only those related to EPL which corresponds to 1678 stays (code GHM 14C05J and 14C05Z). This screening allowed to estimate the distribution, mean and standard error of the cost of a SE.

Integration of data in the model. The decision tree is constructed after integration of calculated parameters. The probability of success or failure of the treatment is calculated from the data in the literature review and integrated at each chance node. The costs data are calculated and integrated at each decision node. The effectiveness of the strategy is measured at the terminal node of each branch of the tree.

Thanks to this tree we could calculate the incremental cost effectiveness ratio (ICER) as followed:

$$\text{ICER} = \frac{\Delta\, cost}{\Delta\, efficacy} = \frac{(cost\ strategy\ MF{+}MS){-}(cost\ strategy\ MS\ alone)}{(efficacy\ MF{+}MS){-}(efficacy\ MS\ alone)}$$

Sensitivity analyses

In cost-effectiveness analysis, sensitivity analyses allow to take into account the uncertainty of the studied parameters by varying their values to evaluate the robustness of the results.

Univariate deterministic sensitivity analysis. One model parameter is varied at a time; all other parameters being kept at their average value. This approach quantifies the uncertainty associated with the data sources that informed the model. We choose to present the results by a Tornado diagram allowing to visualize the hierarchy of the tested variables according to their impact on the ICER. To build this diagram, an uncertain parameter is selected. The analysis is performed on the defined minimum plausible value of this parameter (the lower limit of the 95% confidence interval for the mean) then the analysis is repeated with the maximum plausible value (the upper limit of the 95% confidence interval for the mean). In the same way, each uncertain parameter is studied.

Multivariate probabilistic sensitivity analysis. This approach aims to explore the overall statistical uncertainty generated by the statistical variability of the point estimates of the model variables. We use second-order Monte Carlo simulations to diffuse uncertainty into the model. At each simulation, the values of parameters are drawn from well suited distributions (e.g. beta distribution for probabilities, gamma distribution for costs...). Results of the probabilistic sensitivity analysis are presented in a scatterplot.

RESULTS

Literature review

After screening 3950 results, 36 articles were analyzed, 12 evaluated in detail and 5 selected (4–8). Summary of included studies are presented in **Table 1**. Through this review 1334 women are considered, 657 treated with MF + MS and 677 with MS alone. In each study, baseline characteristics are similar.

Table 1. Literature review.

Author	Grønlund	Stockheim	Schreiber	Sinha	Chu
Year	2002	2006	2018	2018	2020
Nationality	Denmark	Israel	USA	India	UK
Type of study	Prospective crossover	RCT	RCT	RCT	RCT
No. of patients	127 (+49 SE)	115	297	90	705
Protocol - MF (mg) PO + MS (µg) - MS alone (µg) - Other	**MS vaginal** MF 600 + 400 72h +/ 200 2h 400 +/ 200 SE	**MS oral** MF 600 +/ 400 x2 400 x2 +/ 400 x2	**MS vaginal** MF 200 + 800 24h +/ 800 Day 3 800 +/ 800 Day 3 Day 3 : SE or Expectant	**MS different routes** MF 200 + 800 PV 48h +/ 400-800 PO 4h 800 PV 48h +/ 400-800 PO 4h MF or placebo	**MS different routes** MF 200 +/ 800-3200 48h 800 – 2400 MF or placebo
Control Time	Day 8	Day 10-14	Day 8 and 30	Day 14	Day 7
Outcome	Need of SE	Need of SE	complete uterine evacuation	complete uterine evacuation	complete uterine evacuation
Success US : TED	< 20 mm	< 15 mm	Not precise	< 15mm	< 20mm

Estimates of effectiveness

Data for effectiveness are calculated from data of each study selected, results are reported in **Table 2**.

Table 2. **Estimates of effectiveness**.

MF + MS effectiveness step 1						
author	success	Failure	Total	Rate	Detail Failure	SE
Gronlund	29	25	54	53,70%	13 additionnal dose + 12 SE	12
Stockheim	2	56	58	3,45%	46 expectation +10 SE	10
Sinha	32	13	45	71,11%	13 additionnal dose + 0 SE	0
Schreiber	124	24	148	83,78%	13 expectation + 7 additionnal dose + 4 SE	4
Chu	256	96	352	72,73%	50 additionnal dose + 46 SE	46
total	443	214	657	67,43%		72

MS alone effectiveness step 1						
author	success	Failure	Total	Rate	Detail Failure	SE
Gronlund	22	51	73	30,14%	43 additionnal dose + 8 SE	8
Stockheim	9	48	57	15,79%	36 expectation + 12 SE	12
Sinha	6	39	45	13,33%	39 additonnal dose + 0 SE	0
Schreiber	100	49	149	67,11%	19 expectation + 16 additionnal dose + 14 SE	14
Chu	228	125	353	64,59%	65 additionnal dose + 60 SE	60
total	365	312	677	53,91%		94

MF + MS effectiveness step 2				
author	success	Failure = SE	Total	Rate
Gronlund	11	2	13	84,62%
Stockheim	36	10	46	78,26%
Sinha	7	6	13	53,85%
Schreiber	11	9	20	55,00%
Chu	37	13	50	74,00%
total	102	40	142	71,83%

MS alone effectiveness step 2				
author	success	Failure = SE	Total	Rate
Gronlund	30	13	43	69,77%
Stockheim	33	3	36	91,67%
Sinha	20	19	39	51,28%
Schreiber	13	22	35	37,14%
Chu	37	28	65	56,92%
total	133	85	218	61,01%

> Grønlund: this study compares effectiveness of two different medical treatment MF + MS and MS alone with SE. Thus we only consider data of the medical treatment. In the arm MF + MS 40 out of 54 women have a success (29 after first doses of MS and 11 after new doses), or 74.1% VS 52 out of 73 in the arm MS alone (22 after first doses and 30 after new doses), or 71.2%.

> Stockheim: this study compares effectiveness between MF + MS and MS alone. In this protocol, in the arm MF + MS women take only one dose of MS (800µg) while in the arm MS alone they take a new dose in case of failure at 48 hours. In the arm MF + MS 38 out of 58 women have a success (2 after MF and 36 after MS), or 65.5% VS 42 out of 57 in the arm MS alone (9 after one dose and 33 after new dose), or 73.7%.

> Sinha: this study compares effectiveness between MF + MS and placebo + MS. In this protocol, women are admitted to the hospital 48 hours after taking MF or placebo and one to fourth doses of MS (800µg) are given until clinical expulsion occurred. In the arm MF + MS 39 out of 45 women have a success (32 after first dose of MS and 7 after new doses), or 86.7% VS 26 out of 45 in the arm placebo + MS (6 after first dose and 20 after new doses), or 57.8%.

> Schreiber: this study compares effectiveness between MF + MS and MS alone. In this protocol, in case of failure after first dose of MS, women have the choice between new doses of MS or SE or expectation. In the arm MF + MS 135 out of 148 women have a success (124 after first doses of MS and 11 after new doses), or 91.2% VS 113 out of 149 in the arm MS alone (100 after first doses and 13 after new doses), or 75.8%.

> Chu: this study compares effectiveness between MF + MS and placebo + MS. In this study, the primary outcome is failure of the treatment within 7 days after random assignment. Thus, even when cross-referencing the information in the different tables there were missing data to match the protocol of our study. After contacting the

authors, we obtained complete information on the number of women who received another dose of MS and those who underwent SE after the first and last check-ups. In the arm MF + MS 293 out of 352 women have a success (256 after first dose of MS and 37 after new doses), or 83.2% VS 265 out of 353 in the arm placebo + MS (228 after first dose and 37 after new doses), or 75.1%.

From data collected, the probability of success with the treatment after MF + MS (first dose), is estimated to 0.6743; the probability of success with the treatment after MS alone (first dose), to 0.5391; the probability of success with the treatment after MF + MS (second dose), to 0.7183 and the probability of success with the treatment after MS alone (second dose), to 0.6101. In the probabilistic sensitivity analysis, probabilities are assumed beta distributed.

Estimates of costs

Results are reported in **table 3**.

Table 3. Estimates of costs.

	event	cost €	distribution	mean	standard error	references
Visit				173,14		
US		56,70	not varied			CCAM
Consultation	28	25,42	Beta	116,44	2,90	local sources
Resident	26	27				
Senior	2	52				
Sunday	3	40				
Night	1	35				
Medication						
MF		17,97	not varied			local sources
MS			multi	14,38	0,16	local sources
400	71	6,17				
800	961	12,34				
1200	25	18,51				
1600	187	24,68				
2000	2	30,85				
2400	21	37,02				
SE				2605,38		
Anesthesia consultation		25	not varied			local sources
Biology		60	not varied			local sources
Hospital stay	1678		Gamma	2520,38	16,35	CCAM / ENC / local sources
minimum cost		321,1				
maximum cost		580421,2				

We collected 28 consultations including diagnosis and follow-up. Among these consultations 26 were performed by a resident, 2 by a senior and 4 consultations were

increased because they were performed on Sundays or at night. The cost of an ultrasound which was fixed at 56.70 €, cost set by the French health insurance fund (code CCAM: ZCQJ006, since 2005). The total cost of a visit has a mean of 116.44€ (standard error = 2.90€).

The cost of medication includes MF and MS. The cost of MF is fixed since only one dose of 200mg is considered and set at 17.97€. Knowing that a tablet of 400µg costs 6.17€ we establish that the cost of MS has a mean of 14.38€ (standard error = 0.16€).

The cost of SE includes an anesthesia consultation with a biology and a hospital stay (hospitalization and surgical procedure). The cost of anesthesia consultation and biology do not vary and is fixed at 25€ and 60€ respectively.

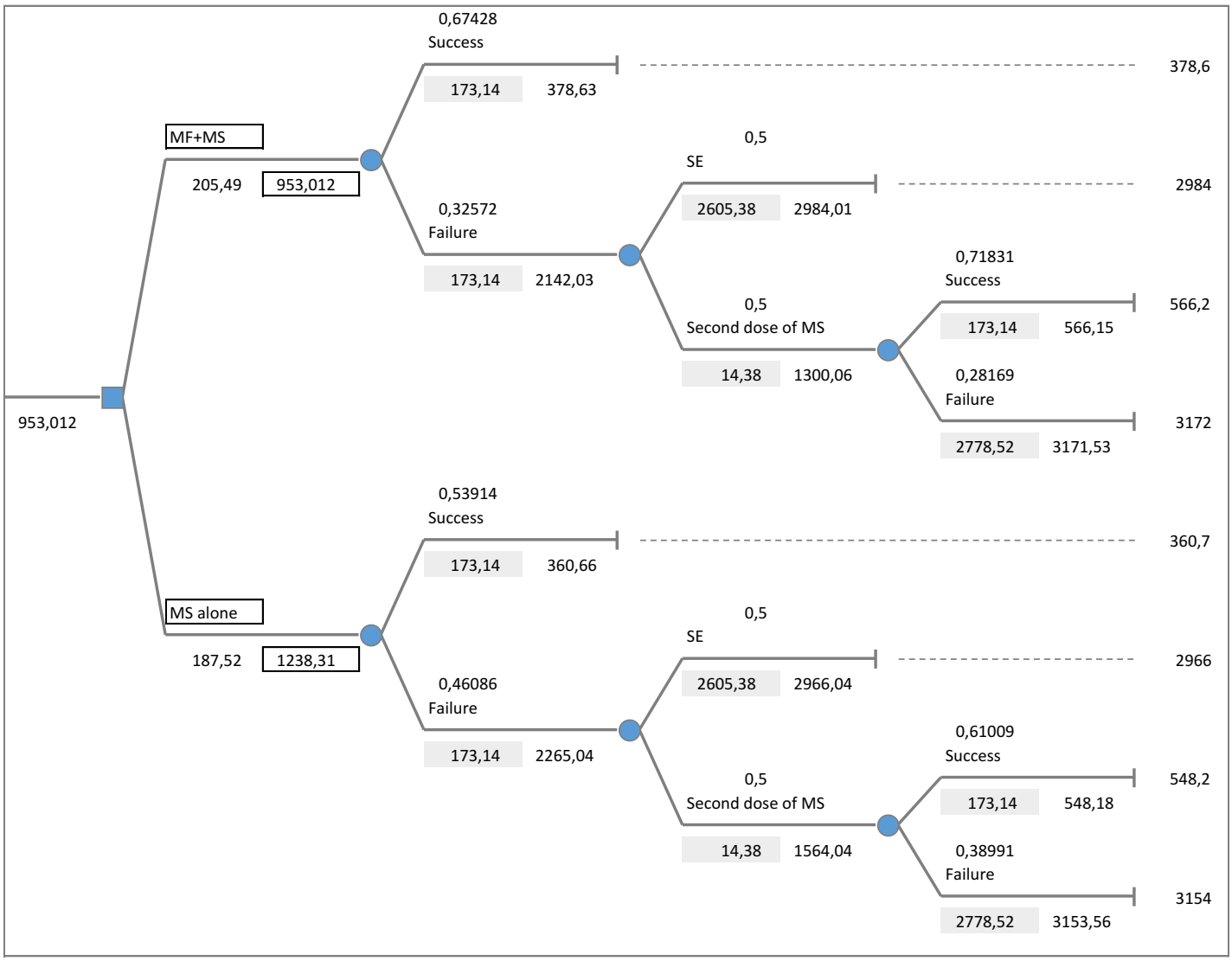
The cost of SE has a mean of 2520.38€ (standard error = 16.35€). In the probabilistic sensitivity analysis, cost of hospital stay for SE in EPL is assumed to be gamma distributed.

Integration of data in the model

Results are reported in **Figure 4**.

If a failure is observed after a first dose of MS women has the choice between take new doses of MS or undergo a SE. Since there is no data in the literature concerning the proportion of women choosing SE rather than medical treatment, we chose an arbitrary probability of 50% in the base case analysis. This probability seems consistent with our observations in clinical practice. In order to test the uncertainty of this parameter, we make this probability varies from 20 to 80% in the sensitivity analysis.

Figure 4. Decision Tree.



Base case analysis

The effectiveness of MF + MS and MS alone strategies are estimated to 0.7913 and 0.6797 respectively. The cost is 953.01€ for MF + MS and 1238.30€ for MS alone. The ICER is calculated as the ratio $\frac{953.01-1238.30}{0.7913-0.6797}$ = - 2557.86€. The ICER is negative since MF + MS is more effective and less costly than MS alone. In others words, MF + MS strictly dominates MS alone.

Deterministic sensitivity analysis

We explore the impact of seven parameters on the ICER results: probability of success of the strategy MF + MS after first dose of MS, probability of success of the strategy MS alone after first dose of MS, probability of success of the strategy MF + MS after second dose of MS, probability of success of the strategy MS alone after second dose of MS, cost of visit, cost of MS and cost of SE, see **Table 4** and **Figure 5**.

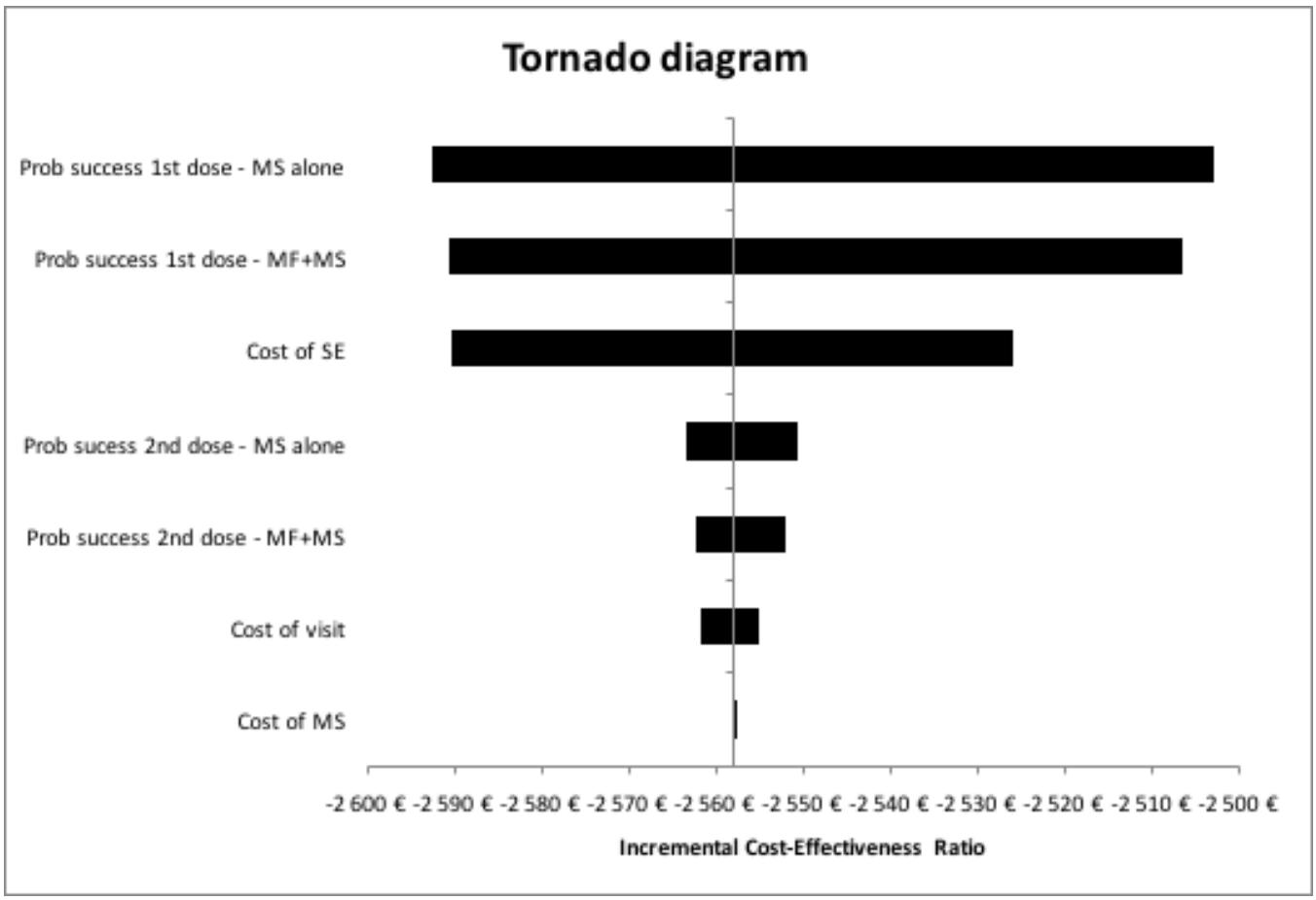
Table 4. Parameters integrated in the Tornado Diagram

Parameters	Mean	Range (minimum – maximum)	Lower Input value ICER	Upper Input value ICER
Probability of success 1st dose – MF + MS	0.6743	0.6379 – 0.7097	-2506.58	-2590.64
Probability of success 1st dose – MS alone	05391	0.5016 – 0.5763	-2592.45	-2502.85
Probability of success 2nd dose – MF + MS	0.7183	0.6429 – 0.7895	-2551.98	-2562.34
Probability of success 2nd dose – MS alone	0.6101	0.5454 – 0.6737	-2563.47	-2550.67
Cost of visit (IC 95%)	116,44 €	111.70 – 122.96	-2554.99	-2561.81
Cost of MS (IC 95%)	14,38 €	14.07 – 14.69	-2557.68	-2558.06
Cost of SE (IC 95%)	2520,38€	2488.62 – 2552.95	-2557.68	-2558.06

This sensitivity analysis reveals that three parameters have the greatest impact on the ICER: the probability of success with the treatment after MS alone (first dose), the probability of success with the treatment after MF + MS (first dose) and the cost of SE. However, the ICER remains constantly negative meaning that the conclusion of the base case analysis is kept unchanged.

ICER slightly increases as the percentage of women switching to SE after medical treatment failure (first dose): from -2629.02€ for 20% to -2502.74€ for 80%.

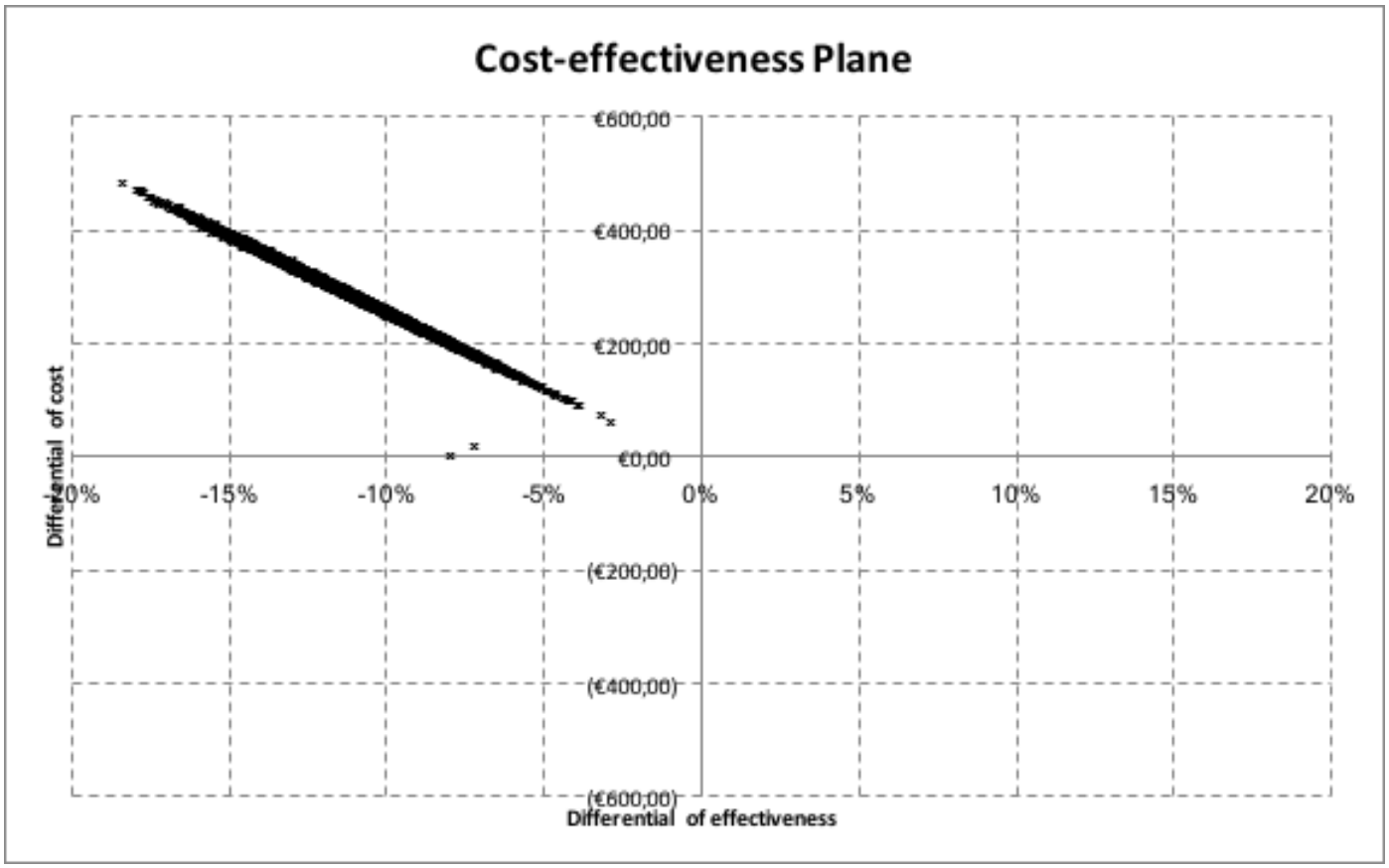
Figure 5. Tornado diagram



Probabilistic sensitivity analysis

Over the 10,000 second-order Monte Carlo stimulations, the effectiveness of MF + MS and MS alone is estimated to 0.7913 (95% CI: [0.7656 ; 0.8166]) and 0.6798 (95% CI: [0.6487 ; 0.7093]) respectively. Cost is 952.83 € for MF + MS (95% CI: [882.18 ; 1025.67]) and 1 238.25 € for MS alone (95% CI: [1156.91 ; 1324.21]). The ICER is -2557.96€ (95% CI: [-2613.66 ; -2461.56€]). Strategy MF + MS is more effective and less costly than MS alone in 100% of simulations, see **Figure 6**. The same conclusion is reached whatever the percentage of women switching to SE after medical treatment failure (first dose).

Figure 6. ICER scatterplot after 10,000 second order Monte Carlo simulations.



DISCUSSION

Main findings

This cost effectiveness analysis demonstrates that MF + MS strictly dominates MS alone in base case analysis with an effectiveness of 79% (95% CI 0.76 – 0.81) VS 68% (95%CI 0.65 – 0.71) and a cost of 953.01€ (95% CI 712.34 to 1273.32€) VS 1238.30€ (95%CI 866.63 to 1721.28€). This conclusion is robust in sensitivity analysis.

Interpretation

Similar results are demonstrated in other studies (10–12). Recently, Hamel et al. (13) lead a double-blind placebo RCT (Trip M trial) with 344 women and observe a difference of 20.4% (136 women 79.1% VS 101 women 58.7%, p=0.000). This result is consistent with our findings although there is a 10% difference in effectiveness for MS alone. This difference might be explained by the expectant attitude. Indeed, waiting one week before introducing misoprostol decreases its effectiveness (14,15). However, this observation alone does not explain this difference because 62% of the population in our review benefited from an initial expectant attitude (Grønlund and Chu's population). We nevertheless note a strictly equivalent result for the effectiveness of MF + MS. This could mean that Mifepristone improves the effectiveness of misoprostol even in case of an expectant attitude.

In our study, cost was 953€ for MF+MS and 1238.30€ for MS alone in accordance with previous published studies. In 2021, Quenby et al. (2) compared different care management for EPL through different countries. The direct health service costs ranged from 333€ (298£) to 1589€ (1421£). Drugs price may differ across countries and explain such variation. For instance, according to Berkley et al. (16) MF is more expensive and MS less expensive in US than in France. 91.63$ (78.8€) VS 20.9$

(17.97€) for a tablet of 200mg of MF and 2.95$ (2.58€) VS 14.34$(12.34€) for 800µg of MS. In our study, the difference in cost between medical strategies was 285€, slightly higher than in the cost-effectiveness study performed alongside the Trip M trial by Hamel et al: 134.82€ (95% CI 50.46–219.18, p=0.002) in favor of MF+MS. A secondary analysis demonstrated that there is no significantly difference in productivity costs between MF+MS and MS alone.

This study is designed in a perspective of medical treatment, considering that avoid surgical evacuation is a success. The preference for medical management is supported by several studies comparing medical VS surgical care of EPL (18–20). The decision model of VK Dalton confirmes women preference for medical treatment or expectation compare with surgery (65 VS 35%) (9). To comfort this hypothesis Graziosis lead a study in 2006 where 50% of women choose medical compared with surgical treatment in case of a success rate over 65% (21). Going further, in 2015, E.A. Strand assumes in his editorial that “increasing access to patient’s preferred treatment is not only good patient care, but appears to be cost-saving as well” (22).

It would be interesting to focus on women’s preference regarding the choice of the treatment, not only on effectiveness. According to Farren et al. (23) the experience of an EPL may cause anxiety, depression and even post-traumatic stress symptoms in some women. In the light of these findings, it seems essential to provide the most effective treatment to reduce the psychological impact of this potentially traumatic event. This reflection reinforces the idea that the combination of MF + MS would have a real impact on the psychological condition since it improves effectiveness.

It would be also interesting to evaluate the impact of EPL through quality of life of women. This consideration is currently lacking in literature. In 2020 Nagendra (27) lead

a cost effectiveness analysis using a modified utility score to evaluate the impact of the medical protocol in the management of EPL. Lemmers and al. and Harwood and al. (19,28) also studied the quality of life during the management of EPL but these score were not enough reproducible to use them for a cost-utility analysis.

In their study, Hamel et al. (17) conclude with a secondary analysis that there is no significantly difference in quality of life (SF-6D) between MF+MS and MS alone for women with EPL manage with medical treatment.

Strengths and limitations

This study is original because aims to compare the cost effectiveness of MF+MS vs MS alone. To our knowledge this is the first cost effectiveness analysis comparing MF+MS with MS alone through a literature review. The main strength of this work is the consideration of studies with high level of proof (one prospective crossover and four randomized control trial) gathering data of 1334 women all over the world.

However, our study has limitations. Although EPL are common, there is no consensus definition in the international literature (24). Their management and the criteria for successful of the medical treatment differ from study to study (2,25). Therefore, the comparison between protocols leads to biases inherent to this lack of consensus in the definition.

Costs are estimated in our center only. Costs could vary greatly from one center to another. The study does not incorporate this source of heterogeneity. Generalizability of results is not ensured.

Considering dose of MS, normalization of prescription was difficult because clinical use is different for each woman. Indeed, the dose of MS is taken according to bleeding

quantity which is a subjective data. However, the variability of misoprostol costs remains low (95% CI 14.07 – 14.69€) and has little impact on our result according to our deterministic sensitivity analysis (95% CI: [-2557.68 ; -2558.06€]). Dose of Mifepristone is different in our data base varies from 200 to 600 mg which could influence on the effect of the treatment. However, Schreiber and Chu (biggest population of the data base) use a dose of 200mg which corresponds to our protocol. Moreover, studies in abortion already shown that dose of MF does not have a major effect on the effectiveness (26). We can therefore presume that this effect is transposable to EPL. The probability of taking a new dose of MS after a failure treatment or choose a surgical evacuation was arbitrary estimated to 50%. However, even when varying this probability from 20 to 80% our conclusions remain constant with MF+MS as a dominant strategy.

It would be interesting to evaluate the impact of EPL through quality of life of women. This consideration is currently lacking in literature. In 2020 Nagendra (27) lead a cost effectiveness analysis using a modified utility score to evaluate the impact of the medical protocol in the management of EPL. Lemmers and al. and Harwood and al. (19,28) also studied the quality of life during the management of EPL but these score were not enough reproducible to use them for a cost-utility analysis.

In their study, Hamel et al. (17) conclude with a secondary analysis that there is no significantly difference in quality of life (SF-6D) between MF+MS and MS alone for women with EPL manage with medical treatment.

CONCLUSION

This cost effectiveness analysis performs from a French healthcare perspective encourages the use of Mifepristone as pretreatment for women who choose a medical solution in case of EPL. More studies need to be conducted on this subject to improve the medical care of women expiring pregnancy loss.

DISCUSSION

Cette analyse coût-efficacité démontre que l'association MF + MS domine strictement le MS seul. L'analyse de notre base de données révèle une efficacité de 79% (IC 95% 0,76 - 0,81) VS 68% (IC 95% 0,65 - 0,71) et un coût de 953,01€ (IC 95% 712,34 à 1273,32€) VS 1238,30€ (IC 95% 866,63 à 1721,28€). Cette conclusion est robuste à travers notre analyse de sensibilité.

Des résultats similaires ont été démontrés dans d'autres études (10-12). Récemment, Hamel et al. (13) ont mené un essai randomisé en double aveugle avec placebo (essai Trip M) auprès de 344 femmes et ont observé une différence de 20,4% (136 femmes 79,1% VS 101 femmes 58,7%, p=0,000). Ce résultat est cohérent avec nos conclusions bien qu'il y ait une différence de 10% dans l'efficacité pour MS seul. Cette différence pourrait s'expliquer par l'attitude expectative utilisée dans leur protocole. En effet, attendre une semaine avant la prise de Misoprostol diminue son efficacité (14,15). Cependant, cette observation est insuffisante car 62% de la population de notre base de données a bénéficié d'une attitude expectative initiale (population de Grønlund et Chu). On note néanmoins un résultat strictement équivalent pour l'efficacité de MF + MS. Cela pourrait signifier que la Mifépristone améliore l'efficacité du Misoprostol même en cas d'attitude expectative.

Dans notre étude, le coût était de 953€ pour la stratégie MF+MS et de 1238,30€ pour la stratégie MS seule, ce coût est en accord avec les études publiées précédemment. En 2021, Quenby et al. (2) comparent différentes stratégies de prise en charge de fausses couches à travers différents pays. Les coûts médicaux directs allaient de 333€ (298£) à 1589€ (1421£). Le prix des médicaments peut différer selon les pays et donc

expliquer cette variation. Par exemple, selon Berkley et al. (16), aux États-Unis le coût de la Mifépristone est supérieur à celui de la France 91,63$ (78,8€) VS 20,9$ (17,97€) pour un comprimé de 200mg tandis que le coût du Misoprostol est inférieur 2,95$ (2,58€) VS 14,34$(12,34€) pour 800µg. Dans notre étude, la différence de coût entre les stratégies médicales était de 285€. Différence légèrement plus élevée que dans l'étude coût-efficacité réalisée par Hamel et al aux Pays Bas: 134,82€ (95% CI 50,46-219,18, p=0,002) en faveur de MF+MS. Une analyse secondaire a démontré qu'il n'y avait pas de différence significative dans les coûts de productivité (arrêt de travail notamment) entre MF+MS et MS seul.

Cette étude a été conçue dans une perspective de traitement médical, considérant l'éviction du curetage comme un succès. La préférence pour le traitement médical est soutenue par plusieurs études comparant la prise en charge médicale VS chirurgicale des fausses couches précoces (18-20). Le modèle de décision de VK Dalton confirme la préférence des femmes pour le traitement médical ou l'attitude expectative par rapport au curetage (65 VS 35%) (9). Pour conforter cette hypothèse, Graziosis a mené une étude en 2006 où 50% des femmes choisiraient le traitement médical par rapport au traitement chirurgical en cas de taux de réussite supérieur à 65% (21). En 2015, E.A. Strand suppose dans son éditorial que "l'accès au traitement préférentiel du patient n'est pas seulement une amélioration de la pratique médicale, mais aussi une source d'économie de coûts" (22).

Il serait intéressant de se concentrer sur la préférence des femmes en ce qui concerne le choix du traitement, et pas seulement sur l'efficacité. Selon Farren et al. (23), l'expérience d'une fausse couche précoce peut provoquer de l'anxiété, une dépression et même des symptômes de stress post-traumatique chez certaines femmes. À la

lumière de ces résultats, il semble essentiel de fournir le traitement le plus efficace pour réduire l'impact psychologique de cet événement potentiellement traumatisant. Cette réflexion renforce l'idée que la combinaison MF + MS aurait un réel impact sur l'état psychologique puisqu'elle améliore l'efficacité du traitement.

Il serait également intéressant d'évaluer l'impact des fausses couches précoces sur la qualité de vie des femmes. Cette considération fait actuellement défaut dans la littérature. En 2020 Nagendra (27) a mené une analyse coût-efficacité en utilisant un score d'utilité modifié pour évaluer l'impact du protocole médical dans la prise en charge des fausses couches précoces. Lemmers et al. et Harwood et al. (19,28) ont également étudié la qualité de vie lors de cette prise en charge mais ces scores n'étaient pas suffisamment reproductibles pour les utiliser dans une analyse coût-utilité.

Dans leur étude, Hamel et al. (17) concluent dans une analyse secondaire qu'il n'y a pas de différence significative en terme de qualité de vie (score SF-6D) entre MF+MS et MS seul pour les femmes endurant une fausse couche avec un traitement médical.

Cette étude est originale car elle vise à comparer le rapport coût-efficacité de l'association MF+MS par rapport à MS seul. A notre connaissance, il s'agit de la première analyse coût-efficacité comparant MF+MS à MS seul à travers une revue de la littérature. La principale force de ce travail est la prise en compte d'études à haut niveau de preuve (un essai croisé prospectif et quatre essais contrôlés randomisés) rassemblant les données de 1334 femmes dans le monde entier.

Cependant, notre étude présente des limites. Bien que les fausses couches soient fréquentes, il n'existe pas de définition consensuelle dans la littérature internationale (24). Leur prise en charge et les critères de réussite du traitement médical diffèrent

d'une étude à l'autre (2,25). Par conséquent, la comparaison entre les protocoles entraîne des biais inhérents à cette absence de consensus dans la définition.

Les coûts sont estimés uniquement dans notre centre. Les coûts peuvent varier fortement d'un centre à l'autre et notre étude n'intègre pas cette source d'hétérogénéité. La généralisation des résultats n'est donc pas assurée.

Concernant la dose de misoprostol, sa standardisation a été difficile car la posologie est différente pour chaque femme. En effet, la dose de misoprostol est prise en fonction de la quantité de saignement dont la donnée reste subjective et mal renseignée dans les études. Cependant, la variabilité des coûts du misoprostol reste faible (IC 95% 14.07 - 14.69€) et a peu d'impact sur notre résultat selon notre analyse de sensibilité déterministe (IC 95% : [-2557.68 ; -2558.06€]). La dose de mifépristone est différente dans notre base de données, variant de 200 à 600 mg, ce qui pourrait influencer l'effet du traitement. Cependant, Schreiber et Chu (population les plus importantes de la base de données) utilisent une dose de 200mg ce qui correspond à notre protocole. De plus, des études dans l'interruption volontaire de grossesse ont déjà montré que la dose de mifépristone n'a pas d'effet majeur sur l'efficacité du traitement (26). Nous pouvons donc supposer que cet effet est transposable à la fausse couche précoce.

La probabilité de prendre une nouvelle dose de misoprostol après un échec du traitement ou de choisir un curetage a été arbitrairement estimée à 50%. Cependant, même en faisant varier cette probabilité de 20 à 80%, nos conclusions restent constantes avec la stratégie MF+MS comme stratégie dominante.

CONCLUSION

Cette analyse coût-efficacité réalisée dans une perspective de santé publique française encourage l'utilisation de la Mifépristone comme traitement préliminaire pour les femmes qui choisissent une prise en charge médicale en cas de fausse couche précoce. D'autres études doivent être menées sur ce sujet afin d'améliorer la prise en charge médicale de cette première complication de la grossesse.

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Titre de la thèse : Evaluation de l'association de Mifépristone et Misoprostol en comparaison du Misoprostol seul dans la prise en charge médicamenteuse des fausses couches précoces : une étude coût efficacité.

Thèse - Médecine - Lille 2022

Cadre de classement : Gynécologie Obstétrique

DES: Gynécologie Obstétrique

Mots-clés : coût-efficacité, fausse couche précoce, traitement préalable par Mifépristone, association à la Mifépristone, traitement combiné, traitement médical, curetage

Résumé :

Contexte : La fausse couche précoce est la première complication de la grossesse touchant 25% des femmes et entraînant des coûts de santé importants. Ce travail vise à évaluer le rapport coût-efficacité de deux stratégies dans la prise en charge médicale des fausses couches précoces en France : Mifépristone + Misoprostol (MF+MS) VS Misoprostol (MS) seul.

Méthodes : Un modèle d'arbre de décision a été construit pour comparer ces deux stratégies. La stratégie évaluée était le protocole appliqué à Lille, France. Les données ont été extraites de cinq études (essai randomisé et étude prospective croisée) issues d'une revue systématique de la littérature réalisée entre 2000 et 2021. L'objectif principal était l'expulsion du sac gestationnel sans curetage chirurgical. Le résultat a été exprimé sous la forme du ratio différentiel coût-efficacité (RDCR). Des analyses de sensibilité déterministe et probabiliste ont été réalisée pour évaluer l'incertitude de ce modèle.

Résultats : 1334 femmes ont été considérées, 657 traitées par MF+MS et 677 par MS seule. L'efficacité du MF+MS est supérieure à celle du MS seul 79%(IC 95% 0,76 - 0,81) VS 68%(IC 95% 0,65 - 0,71) avec des coûts inférieurs 953.01€ (IC 95% 712,34 à 1273,32€) VS 1238,30€ (IC 95% 866,63 à 1721,28€). Le RDCR calculé est de -2557,86€, ce qui signifie que le MF+MS domine strictement le MS seul. Cette conclusion est cohérente avec l'analyse de sensibilité déterministe et probabiliste : ICER -2557.96€ (95% CI : [-2613.66 ; -2461.56€]).

Conclusion : MF+MS est une stratégie plus rentable que MS seul pour la prise en charge médicale des fausses couches précoces d'un point de vue de santé publique français.

Composition du Jury :

Président : Pr Damien SUBTIL

Assesseurs : Dr Benoît DERVAUX, Dr Sophie DELPLANQUE, Dr Victoire DELPORTE
Directeur de thèse : Pr Charles GARABEDIAN