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Cost-utility of a first-trimester screening strategy versus the standard of care for nulliparous women to prevent pre-term pre-eclampsia in Belgium

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ABSTRACT

Objectives: To assess the cost-effectiveness of the Fetal Medicine Foundation (FMF) combined first-trimester pre-eclampsia (PE) screening algorithm, coupled with low-dose aspirin treatment in high-risk patients, compared to the standard of care (SOC; screening based on maternal risk factors) for nulliparous pregnancies in Belgium.
Study design: A decision analytic model was used to estimate the costs and outcomes for patients screened using the SOC and for those using the FMF screening algorithm, from the Belgian payers' perspective. Where possible, the probabilities and associated costs at each decision point were calculated based on published literature and public databases.
Main outcome measures: Cost-effectiveness was assessed using an incremental cost-effectiveness ratio. One-way sensitivity analyses were performed to assess the impact of independent variations in each model parameter. A probabilistic sensitivity analysis was used to estimate the impact of the overall uncertainty of the model on the estimated cost-effectiveness.
Results: Considering an estimated 51,309 pregnancies in nulliparous women in Belgium per year, the FMF screening algorithm resulted in fewer cases of pre-term PE compared with the SOC (479 versus 816 cases) and a cost saving of €28.67 per patient. The outcome in quality-adjusted life-years was similar for both screening approaches (FMF screening algorithm 1.8521 versus SOC 1.8518). The FMF screening algorithm was cost-saving and more effective in 99.4% of simulations.
Conclusions: The FMF screening algorithm coupled with early intervention using low-dose aspirin has the potential to prevent an additional 337 cases of pre-term PE per year compared with the current SOC in this population, along with a cost saving.

1. Introduction

Pre-eclampsia (PE) is a leading cause of maternal and fetal morbidity, long-term disability, and death, affecting 2–8% of pregnancies and causing 20–25% of perinatal deaths [1–4]. Adverse fetal outcomes and maternal complications are inversely related to the gestational age at pre-eclampsia onset [5–12]. Prophylactic aspirin administration has been shown to significantly reduce the incidence of pre-term PE (gestational age at delivery < 37 weeks) and associated complications [13–15], thus early identification of high-risk

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; FMF, The Fetal Medicine Foundation; FPR, false-positive rate; ICER, incremental cost-effectiveness ratio; MAP, mean arterial blood pressure; MF, maternal factors; NICE, National Institute for Health and Care Excellence; NICU, neonatal intensive care unit; OWSA, one-way sensitivity analyses; PE, pre-eclampsia; PlGF, placental growth factor; PSA, probabilistic sensitivity analysis; QALYs, quality-adjusted life-years; SOC, standard of care; UtA-PI, uterine artery pulsatility index; WHO, World Health Organization.

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pregnancies is key to reducing the burden of pre-term PE by allowing accurate targeting of prophylactic aspirin.

In Belgium, the incidence of PE was 2.5% (unpublished data; FPS Public Health, 2017); risk of PE is identified during the first obstetric appointment through evaluation of maternal risk factors (MF), including obstetric and medical history. The absence of national guidelines for PE screening [16] has resulted in wide variability in clinical practice and limited predictive accuracy. According to the International Federation of Gynecology and Obstetrics (FIGO) guide for first-trimester screening and prevention, recognition of MF alone is insufficient for the effective prevention of PE; it recommends a combined risk assessment in which MF are evaluated alongside biophysical and biochemical markers, including mean arterial blood pressure (MAP), uterine artery pulsatility index (UtA-PI), and placental growth factor (PlGF) [17].

The screening algorithm of The Fetal Medicine Foundation (FMF) combines MF, MAP, UtA-PI, and PlGF at 11–13 weeks' gestation to predict the risk of PE [18]. Studies have reported a PE detection rate of $\geq$ 75% for deliveries at < 37 weeks' gestation at a false-positive rate (FPR) of 10% [18–25]. These results are superior to those achieved using MF alone [20].

PE places a significant burden on healthcare systems [26]. According to Ortved and co-authors, in Canada, the FMF screening algorithm coupled with low-dose aspirin has the potential to prevent a significantly greater number of early-onset PE cases, with a substantial cost saving to healthcare systems [27].

The objective of this study was to assess the cost-effectiveness of the FMF screening algorithm, coupled with low-dose aspirin treatment for high-risk patients, for nulliparous pregnant women in Belgium. The analysis compares, from the Belgian payers' perspective, the FMF strategy to the standard of care (SOC) of screening based on maternal factors. This study considered first pregnancies only, since first pregnancy is a risk factor for PE, with a reported incidence up to 3-fold higher than subsequent pregnancies [28].

2. Materials and methods

2.1. Model structure

A decision analytic model was used to estimate the costs and outcomes for patients screened using the SOC (Fig. 1a) versus the FMF screening algorithm (Fig. 1b). The pathways for both screening options were organized according to test results, test sensitivity/specificity, the aspirin prescription rate, the preventative effectiveness of aspirin, and the onset of PE and its development as term PE ($\geq$37 weeks' gestation) or pre-term PE (<37 weeks' gestation). The detection rate (sensitivity) for the FMF screening algorithm was calculated as a weighted average of results from the three relevant studies, with a fixed FPR of 10% (90% specificity) [18,19,25]. The sensitivity and specificity of the SOC approach were calculated from data reported in one of these studies [25], based on the use of MF by obstetricians following the National Institute for Health and Care Excellence (NICE) guideline. The values required to calculate pathway probabilities in the decision analytic model are described in Table S1.

The clinical efficacy of prophylactic aspirin in early pregnancy for the prevention of PE is based on the dosage used [29]. Currently, in Belgium, obstetricians follow World Health Organization (WHO) recommendations for low-dose usage and prescribe 80 mg/day aspirin, which has an effectiveness of around 14% [30,31]. By adopting the FMF screening algorithm and following the FIGO recommendations [17], aspirin will be prescribed at a dose of 150 mg/day or more. The efficacy, used in our model, of 150 mg/day aspirin was based on data from ASPRE, a large multicenter randomized controlled trial in 1776 women with singleton pregnancies at high risk of pre-term PE [14]. The trial reports that aspirin at a dose of 150 mg/day, taken from 11 to 14 weeks until 36 weeks' gestation, reduced the risk of pre-term PE by 62% [14]. Currently, the decision to prescribe aspirin is based on the clinical diagnosis made by the obstetrician. This is the reason why our model assumes that, with SOC, 50% of the patients determined as high risk will be treated with aspirin. The implementation of the FMF algorithm will give a clear positive or negative result, improving the aspirin prescription rate to 90%. Assumptions of the aspirin prescription rates were based on the opinion of Belgian experts and informed by published literature from the UK and Canada [25,27,32]. Adherence to aspirin treatment is not included in our modelling.

The clinical symptoms of PE begin to resolve by 6 weeks postpartum [33]. Therefore, the model assumes all disease-specific events resolve within 6 weeks postpartum. A 1-year time horizon, capturing the effect of PE during the pregnancy period and the short-term consequences of

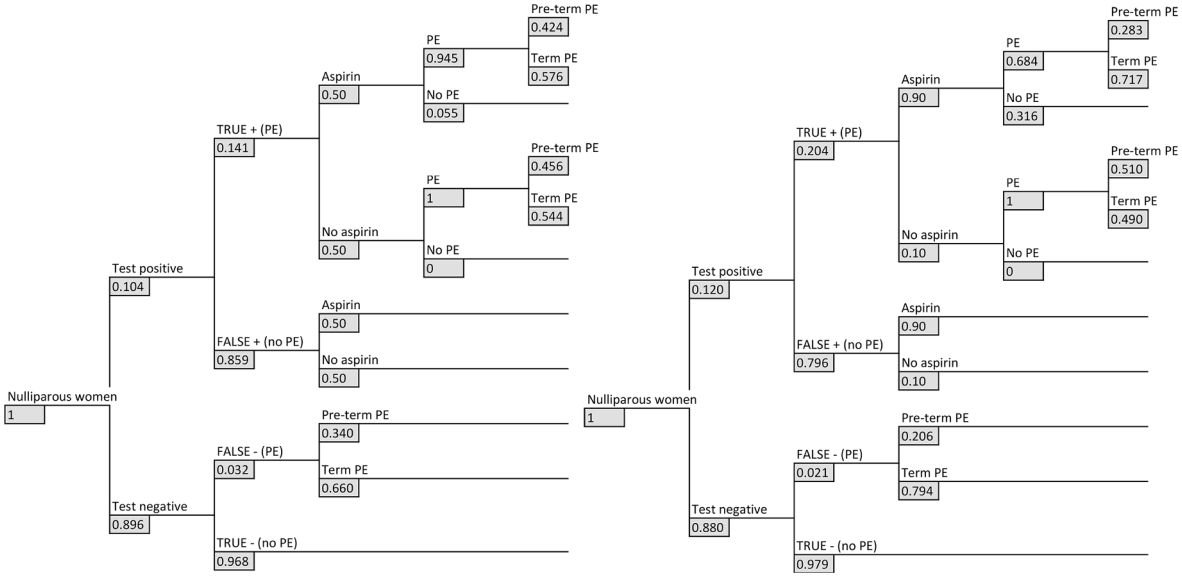

Fig. 1. Decision models of first-trimester screening procedures for PE. Decision tree and probabilities of the possible pathways in (a) the SOC screening approach (screening all pregnant women based on MF alone) and (b) the FMF screening algorithm that includes MF, MAP, UtA-PI and PlGF values. FMF, Fetal Medicine Foundation; MAP, mean arterial blood pressure; MF, maternal factors; PE, pre-eclampsia; PlGF, placental growth factor; SOC, standard of care; UtA-PI, uterine artery pulsatility index.

PE for the mother and child, is used in the base case analysis and thus a discount is not applicable.

2.2. Population

Data on the total number of deliveries (119,102 in 2017) was provided by the Belgian Statistical Office [34], and the proportion of nulliparous pregnancies (43.08% in 2018) was provided by the Centers for Perinatal Epidemiology of Flanders and Wallonia [35,36]. Therefore, this study considers an estimated yearly population of 51,309 nulliparous pregnancies in Belgium; the incidence of PE in nulliparous women is calculated as 4.3% [24]. In Belgium, the rate of pre-term PE is 38% of all PE cases (Table S1).

2.3. Cost effectiveness

Consistent with the Belgian Guidelines for Economic Evaluations and Budget Impact Analyses [37], the cost-effectiveness model accounts for a Belgian public healthcare payers' perspective (costs for the government and patient), and so only direct healthcare costs from the perspective of the healthcare payers are included (Table S2).

Health outcomes for both mother and baby were expressed as quality-adjusted life-year (QALYs), over a 1-year time horizon, based on the utility values shown in Table S3.

Cost effectiveness was assessed using an incremental cost-effectiveness ratio (ICER), which represents the incremental cost per additional unit of outcome achieved between the competing interventions (SOC versus the FMF screening algorithm). Results were presented as the theoretical number of PE cases prevented per year in Belgium, along with the associated cost in Euros (€). One-way sensitivity analyses (OWSA) were performed, with each input varied by +/- 20%, to assess the impact of independent variations in each model parameter.

A probabilistic sensitivity analysis (PSA), involving 10,000 model replications in which the values of all parameters are allowed to vary simultaneously, was used to estimate the impact of overall uncertainty of the model on the estimated cost-effectiveness results. In the PSA, beta distributions were assigned for probabilities, detection rates, and utilities; gamma distributions were assigned for costs and length of stay; a normal distribution was assigned for life expectancies, average age at birth, and gestational age at delivery. An assumed standard error was applied for PSA parameters where this information could not be obtained or calculated from published literature. Since the Belgian Nomensoft database [38] provides fixed tariffs and co-payments for every service charged towards the government or patient, monitoring unit costs and hospitalization fees paid by the patient remained fixed.

The prescription rate of aspirin is one of the parameters with the greatest impact on the ICER. As this parameter had to be assumed based on published literature from the UK and Canada [25,27,32], and the opinion of Belgian experts, sensitivity analyses were performed varying the prescription rates of aspirin to assess the impact on the study results. Firstly, the prescription rate of aspirin in current practice was varied from 10% to 90% and the impact on the ICER measured; secondly, the prescription rate of aspirin upon introduction of the FMF screening algorithm was assessed, starting from the 50% value used in the base case analysis and varied until 90%. A second analysis was performed where this parameter was varied from 10% to 90%.

For all costs that were not calculated using current prices, the appropriate Health Index figures were used to adjust for inflation for the year 2019 [39]. All analyses were performed using Microsoft Excel 2018. Our research did not involve human participants and, therefore, institutional review board approval was not necessary.

3. Results

3.1. Base case analysis

The results from the base case analysis are presented in Table 1. Based on a yearly population of 51,309 nulliparous pregnancies in Belgium, and using the calculated probabilities and costs, the SOC screening approach resulted in an estimated 2190 cases of PE per year. Meanwhile, the FMF screening algorithm (MF, MAP, UtA-PI, and PlGF), followed by low-dose aspirin treatment in patients determined to be at high risk of pre-term PE, resulted in an estimated 1850 cases per year. Thus, according to the model, implementation of the FMF screening algorithm could prevent an estimated 337 cases of PE in Belgium per year. Since aspirin treatment only affects the rate of pre-term PE, and not term PE [13], these 337 prevented cases can be ascribed to pre-term PE.

According to the deterministic analysis, the FMF screening algorithm provides an overall cost saving of €28.67 per patient compared with SOC. The primary driver of this cost saving is the reduction in neonatal intensive care unit (NICU) costs for patients screened via the FMF screening algorithm. This is because the probability of NICU admission decreases (from 40% to approximately 5%) when pre-term PE is prevented, and the length of stay in NICU is longer for patients with pre-term PE compared with those who do not experience PE (Table S2). When combined with reductions in the cost of delivery and pre-delivery hospitalization, the above cost savings overcome the additional expenses associated with screening using the FMF screening algorithm and the anticipated increase in aspirin prescription. Notably, the risk of stillbirth and neonatal death associated with pre-term PE (Table S2) implies that preventing 337 cases of pre-term PE would prevent approximately 10 stillbirths/neonatal deaths per year in Belgium (11.35 versus 2.12 stillbirths/neonatal deaths for every 337 patients with pre-term PE versus without PE, respectively). Although costs associated with stillbirth, neonatal death, and anti-hypertensive treatment were both smaller with the FMF screening algorithm compared with SOC, their contribution to the overall costs was minor.

Over a 1-year time horizon, the number of QALYs was similar between the FMF screening algorithm and SOC. The total QALYs per patient (the sum of QALYs gained by mother and child) were 1.8521 for the FMF screening algorithm versus 1.8518 for SOC, a difference of 0.0003 QALYs.

3.2. Sensitivity analyses

Results of the deterministic OWSA, in which each individual input was varied by 20%, are presented in Fig. 2. The ICER is most sensitive to

Table 1
Deterministic analysis results – Base case comparing the SOC (screening based on MF) with the FMF screening algorithm.

Cost	SOC	FMF screening algorithm	Difference
Total cost per patient, €	*4446.28*	*4417.61*	*−28.67*
Screening	49.35	89.78	40.43
Aspirin	0.49	2.04	1.55
Antihypertensive treatment	2.72	2.30	−0.42
Monitoring	177.51	177.51	0
Hospitalization prior to delivery	330.98	324.74	−6.24
Delivery	2985.44	2977.43	−8.01
Stillbirth and neonatal death	14.89	14.49	−0.40
NICU	884.90	829.32	−55.58
Total QALYs per patient, n	*1.8518*	*1.8521*	*0.0003*
Maternal QALYs	0.9091	0.9092	0.0001
Child QALYs	0.9427	0.9429	0.0002
Pre-term PE cases per year, n	*816*	*479*	*−337*

FMF, Fetal Medicine Foundation; NICU, neonatal intensive care unit; PE, pre-eclampsia; QALYs, quality-adjusted life-years; SOC, standard of care.

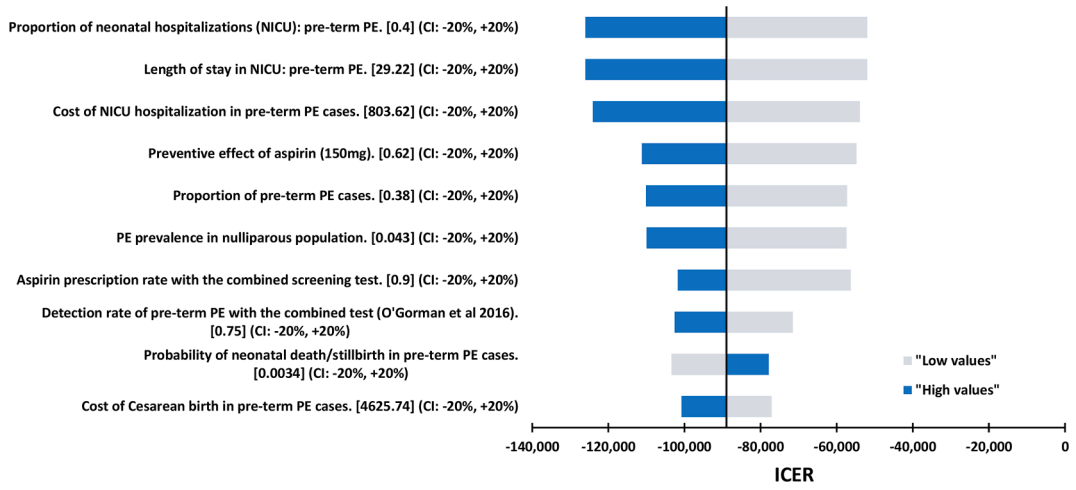

Fig. 2. One-way sensitivity analysis. Tornado diagram showing the effect of input parameters on the ICER, ordered (top to bottom) according to which parameters had the greatest impact. ICER, incremental cost-effectiveness ratio; NICU, neonatal intensive care unit; PE, pre-eclampsia.

length of stay in NICU for patients with pre-term PE, the proportion of NICU admissions for pre-term PE, and the cost of NICU hospitalization. These parameters are all subject to the number of pre-term PE cases that are prevented via implementation of the FMF screening algorithm.

Results of the PSA are displayed in the cost-effectiveness plane shown in Fig. 3. The FMF screening algorithm was the dominant strategy (improved outcomes along with decreased costs) in 99.4% of simulations. All simulations are below the implicit willingness-to-pay threshold of €35,000 used in Belgium.

Sensitivity analysis adjusting the aspirin prescription rate in the SOC model from 10% to 90% demonstrated a smaller, but consistent, cost saving (Table S4). On the other hand, when the prescription rate of aspirin in the first-trimester screening model decreased, the impact on the study results was significant (Table S4).

4. Discussion

This is the first cost-effectiveness analysis of a combined screening approach for PE in nulliparous women, using MF alongside biochemical/biophysical biomarkers as recommended by the FIGO guideline, in a European setting. The model presented here predicts that by accurately identifying patients who will benefit from receiving low-dose aspirin, and by improving the prescription rate and increasing the dosage of aspirin, the FMF screening algorithm will result in more cases of PE being prevented (compared with SOC), with associated benefits for patients and a reduction in costs related to the clinical management of PE.

A cost-effectiveness analysis of the FMF screening algorithm, for first-trimester early-onset PE screening followed by prophylactic aspirin in high-risk patients, has already been conducted in the Canadian healthcare setting [27]. It concluded that the approach has the potential to prevent a significant number of early-onset PE cases with a substantial associated cost saving to the Canadian healthcare system, when compared with the SOC. Notably, the model assumed a 10% aspirin prescription rate for high-risk patients identified through SOC screening which, although very low, is in line with expert opinion on current practice in Canada. In contrast to the Canadian model, we assumed an aspirin prescription rate of 50% in high-risk patients identified through SOC screening. Since this is markedly higher than the Canadian model [27], the threshold for superiority of the FMF algorithm (with regards to

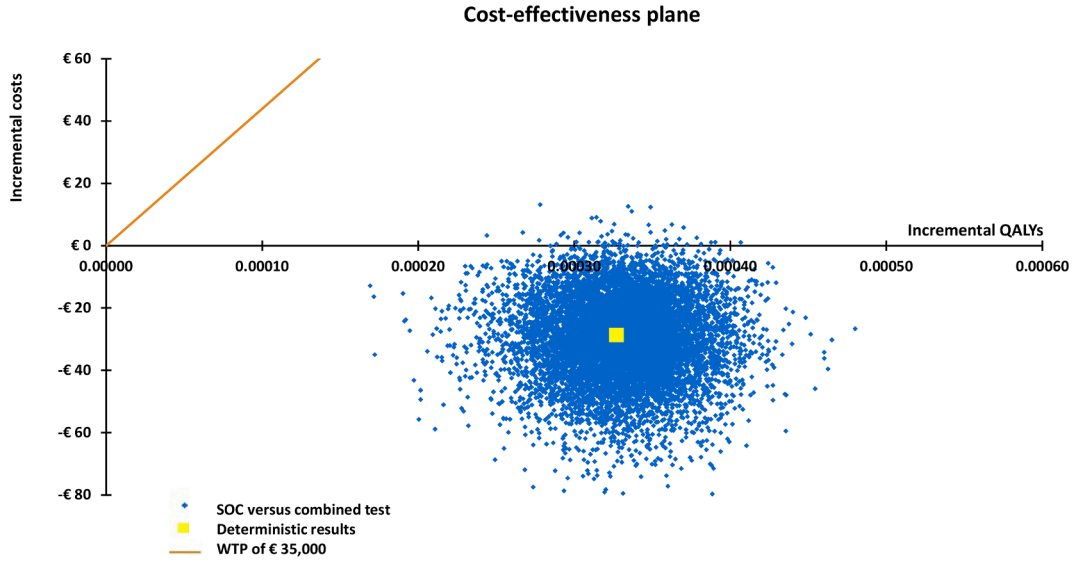

Fig. 3. Probabilistic sensitivity analysis. Results of the probabilistic sensitivity analysis in a cost-effectiveness plane for the FMF screening algorithm compared with SOC. The yellow square represents the results of the deterministic analysis. The implied Belgian willingness-to-pay threshold is represented by the diagonal line crossing the origin. FMF, Fetal Medicine Foundation; QALYs, quality-adjusted life-years; SOC, standard of care; WTP, willingness to pay.

prevention of PE) in our study is higher.

The low cost of aspirin intervention makes it ideal for universal implementation during pregnancy [17]. Recent studies have examined the cost-effectiveness of universal aspirin prophylaxis during pregnancy in the USA and UK/Ireland [40–42]. While they suggest that universal aspirin prophylaxis may be a cost-effective approach for the prevention of PE [40–42], there is concern that overall adherence to aspirin would reduce if it were prescribed without screening [43], especially given its lack of efficacy in low-risk pregnancies [31] and association with vaginal bleeding and postpartum hemorrhage [44], thereby invalidating the adherence assumptions the universal aspirin models are based on. Moreover, many pregnant women would prefer to avoid taking medication during pregnancy [17], which would negatively impact compliance. The existence of a difference between aspirin use in the SOC and the FMF screening approach is supported by real-world data from Canada and the UK [25,45]. Therefore, a targeted approach to aspirin prophylaxis remains a favorable strategy, provided it can be prescribed cost-effectively and based on an accurate test.

The analyses presented here suggest that the combined screening approach using the FMF screening algorithm is the dominant strategy compared with the SOC. In addition, it will prevent an estimated 337 more cases of PE (and an estimated 10 stillbirths/neonatal deaths) per year in Belgium than the current SOC screening procedure. A recent study in the UK evaluated the clinical effectiveness of the FMF screening algorithm and found a significant decrease in the screen-positive rate (8.2% versus 16.1%), and an increase in targeted aspirin use in high-risk patients (99.0% versus 28.9%), in the cohort managed with FMF screening in comparison to the SOC (NICE guidelines) [45]. Evaluation of the relative effect change 21 months post implementation revealed a significant reduction in PE at < 37 weeks (80%, $P = 0.025$) and PE at < 34 weeks (89%, $P = 0.017$). These real-world data from the UK, combined with the present analysis, support the implementation of the FMF screening strategy in public healthcare settings.

Further studies are needed to investigate the current management of PE in Belgium (to account for Belgium-specific population characteristics), robustly assess the sensitivity/specificity of the FMF screening algorithm in the Belgian population, and generate Belgium-specific data for aspirin prescription and the long-term impact of PE on the health of mother and child. Additionally, studies are needed to further investigate the adherence of pregnant patients to aspirin treatment. All of these would help to validate or refine the estimates of cost-effectiveness reported here.

This study has some limitations related to the availability of data and assumptions of the model. Only one reference was identified that was appropriate to calculate the sensitivity and specificity of the maternal factors-SOC approach utilized by gynecologists to identify high risk-patients [25], therefore the outcomes are heavily dependent upon this source. Additional studies are needed to assess the current SOC sensitivity and specificity in Belgium. Furthermore, this study evaluates the use of the FMF screening algorithm in nulliparous women alone, whereas previous validations of the algorithm were conducted in populations composed of nulliparous and parous women. Notably, the utility loss due to PE was calculated based on the pregnancy period. Therefore, even if pre-term PE is more severe than term PE, term PE has a higher utility loss than pre-term PE (since the gestational age at delivery is higher). Due to the 1-year time horizon (rather than a lifetime horizon) there were some costs and health outcomes that were not included in the current model. These include the potential healthcare costs and health loss due to long-term complications of PE (for the mother and child), such as cardiovascular sequelae [46], as well as costs associated with necessary Cesarean deliveries in subsequent pregnancies for patients who experience PE in their first pregnancy. The omission of these costs tends towards an underestimation of the cost savings associated with implementation of the FMF screening algorithm. Conversely, any increase in complications associated with aspirin use and the costs relating to calculation of UtA-PI (which requires additional time and expertise) were not included, which tends toward an overestimation of cost savings associated with the FMF screening algorithm. Inclusion of these costs would reduce cost savings but not eliminate the overall benefit. Regarding dosing protocols, whilst the standard aspirin dosage (SOC) in Belgium is 80 mg/day, the FMF screening algorithm used the 150 mg/day aspirin dose as, due to the ASPRE trial, experts are increasingly using the higher dose. Finally, the model assumes that the aspirin prescription rate in Belgium following SOC screening is 50%. It also assumes that implementing a screening program based on MF combined with specific biochemical/biophysical measurements would increase the prescription rate to 90%. Although these assumptions were validated by Belgian experts, they are not based on published data from Belgian clinical practice.

5. Conclusions

This economic evaluation supports the implementation of the FMF screening algorithm in Belgium as a first-trimester screening approach for PE in nulliparous pregnancies, since it prevents an estimated 337 cases of PE per year, at a cost saving of €28.67 per patient.

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Declaration of Competing Interest

A.D.G is employed by Roche Diagnostics Belgium. K.V was employed by Roche Diagnostics at the time of the study. S.V. reports personal fees from Roche Diagnostics, ThermoFisher Scientific and Alexion outside the submitted work. L.P. reports speaker fees and consultancy from Roche Diagnostics and Ferring Pharmaceuticals, grants from Roche Diagnostics, grants from PerkinElmer and grants from ThermoFisher Scientific outside the submitted work. In addition, L.P. has patent US 8,647,832 and patent EP2245180 issued. L.P. is a trustee of the International Society in Ultrasound in Obstetrics and Gynecology. The remaining authors report no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.preghy.2021.06.012.

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