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Published in:
Journal of Reproductive Immunology

DOI:
10.1016/j.jri.2023.104141

Publication date:
2023

Journal of Reproductive Immunology 160 (2023) 104141

Contents lists available at ScienceDirect

Journal of Reproductive Immunology

journal homepage: www.elsevier.com/locate/jri

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ARTICLE INFO

Keywords:
Cost-effectiveness analysis
Preterm preeclampsia
Netherlands

ABSTRACT

Objectives: The risk of preterm preeclampsia (PT PE) can significantly be reduced by starting acetylsalicylic acid ≤ 16 weeks of gestational age. First trimester predictive models based on maternal risk factors to effectively start this therapy lacked sufficient power, but recent studies showed that these models can be improved by including test results of biochemical and/or -physical markers. To investigate whether testing a biochemical marker in the first trimester is cost-effective in the Netherlands, a cost-effectiveness analysis was performed in this study.
Study design: The outcome of this study was expressed as an incremental cost-effectiveness ratio (ICER) with as effect prevented PT PE cases. To evaluate the impact of each model parameter and to determine model uncertainties, both univariate and probabilistic sensitivity analyses were performed.
Results: When compared to the baseline strategy, the test strategy is estimated to save almost 4 million euros per year on a national scale and at the same time this would prevent an additional 228 PT PE cases. The sensitivity analyses showed that the major drivers of the result are the costs to monitor a high-risk pregnancy and the specificity and that most of the model simulations were in the southeast quadrant: cost saving and more prevented complications.
Conclusions: This study showed that a first-trimester test strategy to screen for PT PE in the first trimester is potentially cost-effective in the Dutch healthcare setting. The fact that the specificity is a major driver of the ICER indicates the importance for a (new) screening model to correctly classify low-risk pregnancies.

1. Introduction

Preterm preeclampsia (PT PE) is a pregnancy related disorders which is associated with short- and long-term complications for both mother and offspring (Bokslag et al., 2016; Rana et al., 2019). Fortunately, meta-analyses and the World Health Organization showed that starting acetylsalicylic acid (ASA) early during pregnancy significantly reduces the incidence of PT PE (Roberge et al., 2018, 2017, 2013). To effectively start this therapy, a good screening method in the first trimester is necessary. Nonetheless, previous predictive models in the first trimester based on maternal risk factors lacked sufficient power to predict PT PE well and multiple studies have already shown that the performance of these models can be improved by including biophysical and/or -chemical markers (Guy et al., 2020; Tan et al., 2018; Kuc et al., 2013; Poon and Sahota, 2019; Bartsch et al., 2016; Verlohren et al., 2022; O'Gorman et al., 2016; Stepan et al.,). Moreover, the International Society for the Study of Hypertension in Pregnancy recently recommended to use multivariable models, including the biomarker placental growth factor (PlGF), to predict the risk of developing PE at 11–14 weeks of gestational age (Magee et al., 2022). In the Netherlands, the early risk assessment for preeclampsia is still based on the guidelines from The National Institute for Health and Care Excellence (NICE), which includes anamnestic and demographic risk factors such as a history of PE in a previous pregnancy, obesity or advanced maternal age (Rana et al., 2019). However, it is suggested that a screening algorithm based on maternal demographic and anamnestic risk factors in

Abbreviations: ASA, acetylsalicylic acid; CI, confidence interval; ICER, incremental cost-effectiveness ratio; PlGF, placental growth factor; PSA, probabilistic sensitivity analysis; PT PE, preterm preeclampsia; RR, relative risk.

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https://doi.org/10.1016/j.jri.2023.104141
Received 2 May 2023; Received in revised form 7 July 2023; Accepted 29 August 2023
Available online 1 September 2023

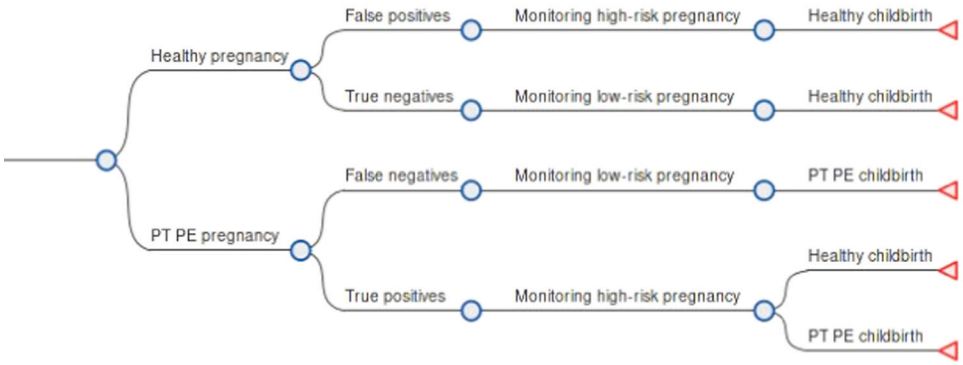

Fig. 1. Decision tree for first trimester screening. Management of low- and high-risk pregnancies and pregnancy outcome in which the true positives and true negatives are determined by, respectively, the analytical parameters sensitivity and specificity.

combination with data from a biochemical marker could also be beneficial in the Netherlands (Zwertbroek et al., 2021).

Testing pregnant women in the first trimester will result in extra obstetrical healthcare costs in the first trimester and additional monitoring during the pregnancy, but, on the other hand, better monitoring and starting an intervention can reduce the number of adverse pregnancy outcomes and save healthcare costs at the end of pregnancy. To investigate whether such a test strategy is cost-effective in the Netherlands, a CEA was performed comparing two screening strategies: the current screening strategy for PT PE based on risk factors (i.e. baseline) versus a test strategy. The current screening strategy consists of a risk-assessment based on only demographic and anamnestic risk factors and the 'test strategy' consists of a screening program in which all pregnant women in the Netherlands are tested in order to combine this information with known demographic and anamnestic risk factors. As demographic and anamnestic risk factors are already registered by default when a pregnant woman enrolls in the Dutch health care system, the test strategy is an add-on to the current screening strategy for preterm preeclampsia. Both screening strategies will categorize women into a low- or high-risk pregnancy and based on this categorization a woman will receive the care as usual/standard care (i.e. low-risk pregnancy) or a healthcare pathway which is equivalent to the care that high-risk pregnancies currently receive, including ASA treatment and more intensive monitoring.

2. Methods

2.1. Model overview

A decision tree model was set up to investigate the cost-effectiveness of each strategy (Fig. 1) (Tran-Duy, 2022). The 'low risk' group will follow standard pregnancy health care in the Netherlands and this care includes appointments with healthcare professionals, hospitalization, if applicable, and medical interventions. The 'low risk' group will also include women who are falsely classified as 'low risk'(i.e. false negative cases) and these women will develop preterm preeclampsia. On the other hand, the 'high risk' group will also include false positive cases.

The outcome of this decision tree model was expressed as an incremental cost-effectiveness ratio (ICER):

$$ICER = \frac{Costs_{Test\ \ strategy} - Costs_{baseline}}{Effect_{Test\ \ strategy} - Effect_{baseline}}$$

As unity for effect, the number of averted PT PE complications was used and the ICER will, therefore, represent the obstetrical costs per averted PT PE case. All costs were indexed to 2019 using the Dutch consumer price index (C.B.v.d.S.S, 2022). The study only focused on the direct obstetrical costs and on the effect of preventing a PT PE complication. Long-term risks and neonatal admission and their associated costs were left out of scope, since these are not related to direct obstetrical costs. The study had a time horizon of a full pregnancy and, because of this, no discounting of costs and effect was applied. In each model 162,146 women were included as this was the total registered number of pregnancies in the Netherlands in 2019 at Perined with a gestational age of $\geq$ 22 weeks at term or a birth weight of $\geq$ 500 g, when gestational age at term was unknown (Perined, 2019). Perined is a collaboration of Dutch professional organizations in perinatal care and it is responsible for the registration of perinatal data in the Netherlands. The incidence of PT PE was extracted from a recent Dutch study focusing on a first trimester screening algorithm for PE and 1.4% of the women developed preterm PE (Zwertbroek et al., 2021).

Table 1
Model parameters.

Model parameter	Value (%)	Reference
Incidence preterm preeclampsia (n = 2270)	1.4	(Zwertbroek et al., 2021)
Baseline screening – Sensitivity	41.0	(Tan et al., 2018)
Baseline screening – Specificity	90.7	(Tan et al., 2018)
Test strategy – Sensitivity (+15%)	56.0	Based on (Guy et al., 2020; Tan et al., 2018; Kuc et al., 2013; Poon and Sahota, 2019; Bartsch et al., 2016; Verlohren et al., 2022; O'Gorman et al., 2016; Stepan et al.,)
Test strategy – Specificity (+5%)	95.7	Based on (Guy et al., 2020; Tan et al., 2018; Kuc et al., 2013; Poon and Sahota, 2019; Bartsch et al., 2016; Verlohren et al., 2022; O'Gorman et al., 2016; Stepan et al.,)
Efficacy ASA treatment	67	(Roberge et al., 2018)

2.2. Model parameters

All model parameters such as costs, treatment efficacy, sensitivity and specificity were extracted from literature and are summarized in Table 1.

The sensitivity and specificity are analytical parameters indicating the percentage of individuals respectively correctly classified as diseased (i.e. true positive) and correctly classified as healthy (i.e. true negative). These analytical parameters are used to stratify pregnant women in the first trimester into a low/standard- or high-risk pregnancy. The baseline sensitivity and specificity for PT PE were extracted from guidelines of the National Institute for Health and Care Excellence (Tan et al., 2018). These guidelines for England and Wales include a screening approach in the first trimester with only anamnestic and demographic risk factors and this is equivalent to the current screening method in the Netherlands. According to these guidelines, women should be considered to be at risk of developing PT PE when they have any major risk

Table 2
Indexed costs (2019) for healthy pregnancies and pregnancies with preterm preeclampsia in the Netherlands.

Model parameter	Costs	Low value	High value	Reference
Screening test	€89	€63	€123	(Schlembach et al., 2018; Chantraine et al., 2021; Shmueli et al., 2012; Dubon Garcia et al., 2021)
Monitoring low-risk pregnancy	€537	€379	€625	(Hendrix et al., 2009)
Childbirth costs healthy pregnancy	€702	€625	€718	(Hendrix et al., 2009)
Monitoring high-risk pregnancy	€2768	€ 1148	€ 4388	(Delahaije et al., 2014)
Childbirth costs preterm preeclampsia	€6345	€ 1618	€ 11,072	(Delahaije et al., 2014)

factor such as history of hypertensive disease in a previous pregnancy, chronic kidney disease, diabetes mellitus or chronic hypertension or more than one moderate risk factor; first pregnancy at age $\geq$ 40 years, body mass index $\geq$ 35 kg/m^2 or family history of PE. Even though there are studies reporting absolute improvements in the sensitivity of more than 30% after including a biochemical marker in prediction models, the added value of the inclusion of a biochemical marker in the current study was set at 15% and 5% for the sensitivity and specificity, respectively (Guy et al., 2020; Tan et al., 2018; Kuc et al., 2013; Poon and Sahota, 2019; Bartsch et al., 2016; Verlohren et al., 2022; O'Gorman et al., 2016; Stepan et al.,). These absolute percentages are a conservative estimate of available data. Further, starting ASA treatment in the first trimester showed a significnat reduction of PT PE. Roberge et al. concluded that the effect of ASA was confined in a specific subgroup and that this effect was a 67% reduction of PT PE (Relative risk (RR) 0.33; 95% confidence interval (CI) 0.19–0.57) in women who started aspirin at $\leq$ 16 weeks of gestation and at a daily dose of $\geq$ 100 mg (Roberge et al., 2018).

2.3. Costs estimations

This study was conducted from a healthcare perspective and only direct costs were included. Also, the time horizon of the analysis was limited to the duration of the pregnancy and therefore, postpartum and/or neonatal costs were disregarded. All costs were extracted from studies focusing on the healthcare system in the Netherlands (Table 2). The costs of a healthy pregnancy were based on a Dutch multicenter prospective nonrandomized study (n = 449 participants) evaluating women with different preferences to give birth: at home or hospital setting (Hendrix et al., 2009). Giving birth in a hospital setting was further divided into two groups; some women were referred to give birth under the supervision of an obstetrician and others delivered under supervision of a midwife. For the latter, women were discharged within a few hours after birth for postpartum home care. The average costs of all three groups was used for the prenatal and childbirth costs of uncomplicated pregnancies and these costs included appointments with healthcare professionals, maternal hospitalization, if applicable, and medical interventions based on standardized healthcare costs (Oostenbrink et al., 2002). The costs of PT PE are based on a retrospective cohort study evaluating both prenatal and childbirth costs for high-risk PE pregnancies in het Netherlands (PreCare study, n = 104 participants) and the study covered the interval from conception until maternal hospital discharge (Delahaije et al., 2014). The prenatal costs included outpatient visits and additional laboratory tests such as ultrasound and automated blood pressure monitoring. Childbirth costs included maternal hospital admission and all costs associated with delivery. These costs did not include any costs associated with neonatal hospital care. Last, the costs of a biochemical screening test were estimated by using the average of various CEAs evaluating the performance of a first trimester screening test based on biochemical markers such as soluble Flt-1, placental protein 13 and/or PlGF in Germany, Israel, Austria, United Kingdom and Belgium, while no price of such test was available for the Netherlands (Schlembach et al., 2018; Chantraine et al., 2021; Shmueli et al., 2012; Dubon Garcia et al., 2021). These biochemical markers are intensively researched for placental-related disorders such as PT PE and are also possible candidate biomarkers that can be included in a first trimester screening test in the Netherlands (Magee et al., 2022; Zwertbroek et al., 2021; Stepan et al., 2022). For a risk-assessment based on biochemical markers, little needs to change on an organizational level in the Netherlands since testing of markers could be combined with or material can be used from the centralized Prenatal Screening Infection and Erythrocyte immunization (PSIE) test. In this screening, the blood group, presence of any antibody and infections are determined and this blood is drawn in the first trimester in already more than 99% of all pregnant women in the Netherlands since 2015 (van der Ploeg et al., 2019). A biochemical test for the prediction of PT PE can be seen as an add-on to this screening program.

2.4. Sensitivity analysis

To evaluate the influence of each model parameter and to determine model uncertainties, univariate and probabilistic sensitivity analyses were performed. In the univariate sensitivity analysis, model parameters with the greatest influence on the ICER were determined by replacing each time one single parameter for its low or high value.

For low and high value of the test price, the lowest and highest costs found in literature for a first trimester screening test were used (Chantraine et al., 2021; Shmueli et al., 2012). In the PreCare study, the standard deviation of all costs is presented and these values were used to calculate the low and high value of the prenatal costs for a high-risk

Table 3
Overview of the number of women (n = 162,146) for each step and costs. Including the difference between the test strategy and the current screening strategy (baseline).

	Test strategy			Baseline			
	n	Costs	Total costs	n	Costs	Total costs	
Monitoring high-risk pregnancies	8146	€2768	€22,547,826	15,799	€2768	€43,732,136	-€21,184,310 (−48.4%)
Monitoring low-risk pregnancies	154,000	€537	€82,698,059	146,347	€537	€78,588,241	+ €4,109,817 (+5.2%)
Preterm preeclampsia childbirth	1418	€6345	€8,999,263	1646	€6345	€10,446,807	-€1,447,545 (−13.9%)
Healthy pregnancy childbirth	160,728	€702	€112,830,829	160,500	€702	€112,670,675	+ €160,154 (+0.1%)
First-trimester screening test	162,146	€89	€14,430,994	-	-	-	+ €14,430,994 (NA)

NA = not applicable

Table 4
Overview of incremental costs and effect and calculated incremental cost and effect (ICER) ratio.

Test strategy		Baseline				
Total costs	Averted complications	Total costs	Averted complications	Incremental costs	Incremental effect	ICER
€241,506,970	852	€245,437,859	624	-€3,930,889	228	Dominant

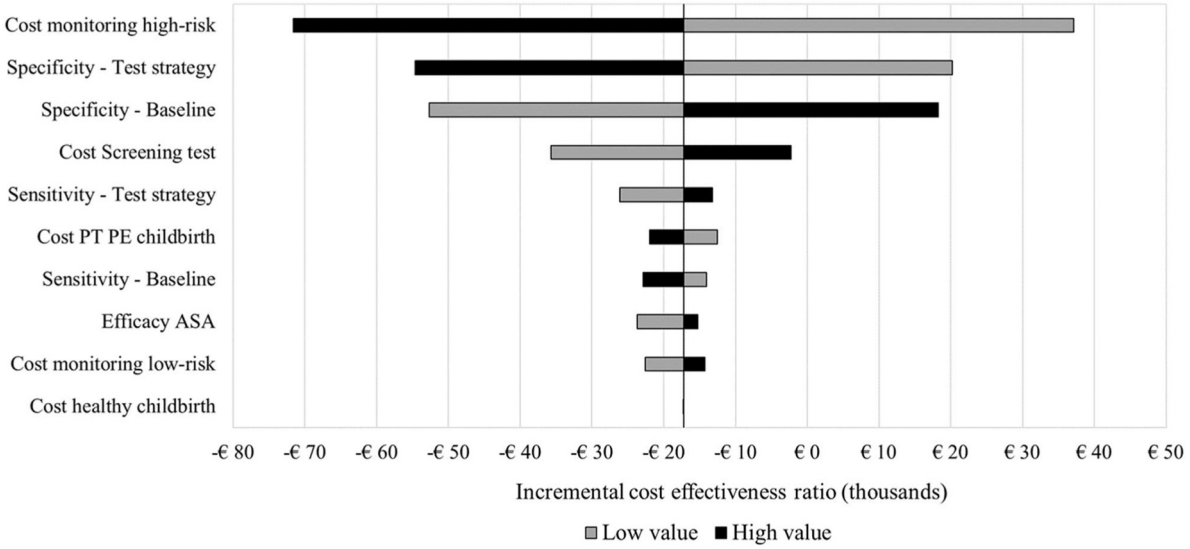

Fig. 2. Tornado plot with results of the univariate sensitivity analysis. Incremental cost-effectiveness ratio (ICER) is presented in costs (thousands) per averted preterm preeclampsia (PT PE) complication through the effect of better monitoring and acetylsalicylic acid (ASA) treatment. Reference ICER of -€17,230 is presented as a solid vertical line. To note; since the ICER is negative, results of the univariate sensitivity analysis cannot be interpreted unequivocally.

pregnancy and the childbirth costs of pregnancies complicated by PT PE (Delahaije et al., 2014). For healthy pregnancies, the average of the "home birth" and "short-stay hospital" was used for the low value and the "short-stay hospital" and "hospital birth" groups for the high value (Hendrix et al., 2009). The impact of ASA treatment was evaluated by using the published efficacy of ASA treatment on the development of PT PE and its confidence interval: 43% and 81% (Roberge et al., 2017). The low and high value for the analytical parameters were calculated for both strategies by using a relative margin of + /− 10% and + /− 2.5% for the sensitivity and specificity, respectively.

In the probabilistic sensitivity analysis (PSA), the impact of joint parameter uncertainty on incremental costs and averted complications was assessed by simultaneously varying all model parameters in a Monte Carlo simulation with 1000 iterations. All involved parameters were randomly varied and sampled from their appropriate distributions: beta distribution for ASA effectiveness, sensitivity and specificity and gamma distribution for all costs. As the test strategy is a screening approach consisting of the standard screening method in combination with an additional biochemical test, the probabilistic values of the sensitivity and specificity for the test strategy were linked to the baseline strategy. Cost-effectiveness planes and acceptability curves were subsequently generated from the Monte Carlo simulation to evaluate the probability that the test strategy was cost-effective over a range of willingness-to-pay thresholds for an averted complication.

3. Results

An overview of the model outcomes is shown in Table 3. The test strategy resulted in less monitoring costs of high-risk pregnancies with a reduction of 48.4% and reduced childbirth costs of PT PE pregnancies; 13.9%. On the contrary, higher costs were observed in monitoring low-risk pregnancies and childbirth cost of healthy pregnancy after a test strategy. Both strategies were subsequently compared by calculating the total incremental costs and incremental effect (Table 4).

When compared to baseline, the test strategy is estimated to save almost 4 million euros per year on a national scale and at the same time this would prevent an additional 228 cases of PT PE.

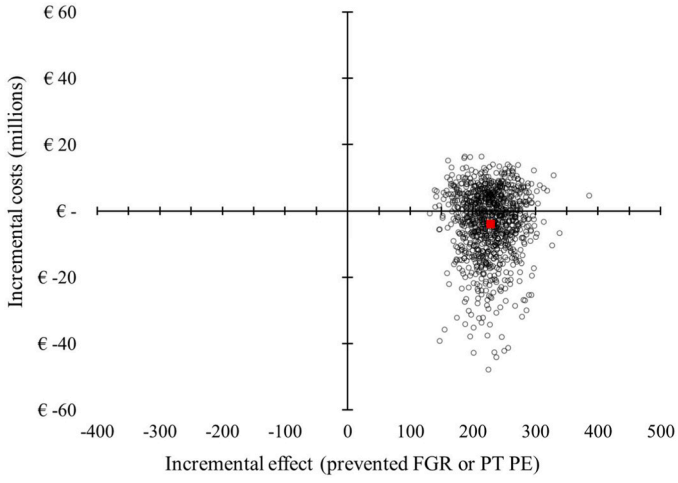

Fig. 3. Cost-effectiveness plane of the universal test strategy versus the baseline strategy. Data were generated through a Monte Carlo simulations with 1000 iterations. Data is presented as costs per averted complication and red square is representing reference ICER. Costs are presented in millions and effect in prevented preterm preeclampsia (PT PE) cases.

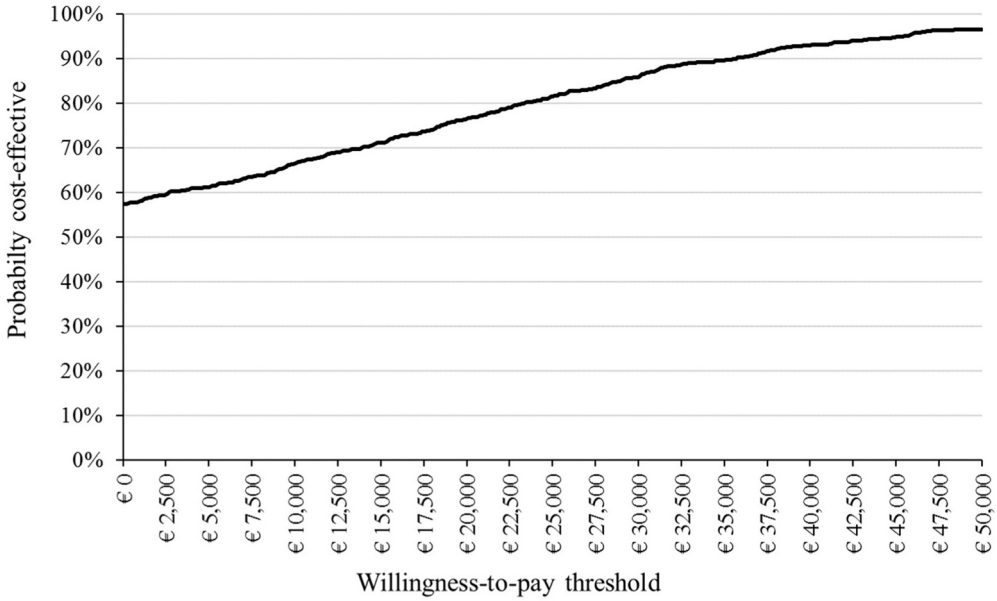

Fig. 4. Cost-effectiveness acceptability curve (CEAC). Curve summarizes the effect of all parameter uncertainties on the probability that the universal test strategy is cost effective when a willingness-to-pay is applied. Willingness-to-pay is presented as costs per averted complication.

3.1. Sensitivity analyses

The Tornado diagram showed that the major influencers of the model are the costs to monitor a high-risk pregnancy and the specificity (Fig. 2).

The results of the PSA showed that all simulations were scattered within the northeast and southeast quadrants and that most of these simulations were in the southeast quadrant: 574 out of 1000 scenarios (Fig. 3). In this quadrant, the test strategy saves costs and averts more PT PE cases. So, with an 57.4% probability the test strategy dominates the baseline strategy. In the other 42.6% simulations, cost-effectiveness depended on the threshold applied: when a willingness-to-pay threshold of €10,000 per averted complication case was used, a majority of the test strategy scenarios would be cost-effective with a cumulative percentage of 66.6%. The probability of cost-effectiveness increased to 96.6% at a threshold of €50,000 per averted complication (Fig. 4).

4. Discussion and conclusion

In this CEA, a decision tree model was established to investigate whether a first trimester test strategy in the Netherlands is cost-effective. The decision model in this study showed that such test strategy is likely dominant, as it would both save costs and prevent complications. However, any CEA is influenced by the uncertainty of its input parameters and because of this, both a univariate and probabilistic sensitivity analyses were performed. The Tornado diagram showed that the costs of monitoring high-risk pregnancies and the specificity of both strategies are major drivers of our ICER's direction. This basically means that the ICER strongly depends on the included number of false-positive cases and the associated monitoring costs of these cases. All three major drivers can result in a positive ICER and pass the threshold of €10,000 per averted complication. This threshold was also used for the willingness-to-pay per averted PE disorder in a publication by other authors (Meads et al., 2008). Noteworthy, this was the lowest evaluated threshold while also thresholds of €50,000 and €100,000 per averted disorder were tested in the study. None of our input parameter uncertainties would cause the ICER passing these thresholds. The fact that the specificity is such a major driver of the ICER in both the baseline and test strategy indicates the importance for a new screening strategy to correctly classify low-risk pregnancy. The reason why the true positive PT PE cases and their reduction at the end of pregnancy through starting ASA have a little influence on our model is, most likely, the fact that their reduction in childbirth costs is relatively small due to the low incidence of PT PE. Numbers of PT PE are ranging from 1% up to even 5%, nonetheless the test strategy remains cost-effective when these PT PE incidence rates are used in our model. Further, the costs of a healthy childbirth have a marginal influence on the results with ICERs ranging from -€ 17,307 to -€ 17,214 for the low and high value, respectively. As PT PE is a pregnancy-related disorder associated with short- and long-term complications for both mother and offspring, averted cases of PT PE might also result in long-term beneficial effects after childbirth. Possibly, the ICER will only become more dominant when long-term effects will be included, as the intervention and associated extra costs (i.e. testing and better monitoring) has already taken place. The approach taken in this study can, thus, be considered conservative, and extending the model may be desirable for more exact estimates. However, it is unknown what the actual effect of preventing a PT PE event is on the long-term and, therefore, such model will also introduce a substantial amount of additional uncertainty.

False-positive classifications might provoke unnecessary anxiety for the parents, but Crombag et al. concluded that Dutch women are positive about a first trimester screening for PE (Crombag et al., 2017). Participants in their study acknowledged that a high-risk categorization could result in anxiety but were convinced that personal and professional interventions would take away this anxiety. Additionally, Simeone et al. demonstrated that a first-trimester preventive program did not result in increased anxiety and that some women even preferred specialized care such as more intensive monitoring (Simeone et al., 2015). They concluded that this, most likely, gives the pregnant women a feeling of tailored care. One could question the need for additional testing when all pregnant women could easily be recommended to start taking ASA in the first trimester. However, there is currently no evidence that a universal ASA prophylaxis will work in terms of therapy compliance and this therapy compliance might even be reduced when a therapy is recommended for everyone without any risk stratification, as suggested by Poon et al (Poon et al., 2019). Their study showed that women in the United Kingdom who were classified as high-risk pregnancy after a risk factor-based prediction had a lower therapy compliance compared to a multivariable test based on risk factors and

biochemical markers with respectively a compliance rates of 28.9% versus 99.0%. This difference in therapy compliance was also observed in other studies (Guy et al., 2020; Tan et al., 2018). This lack of therapy compliance can also be found in the daily intake of folic acid which is recommended four weeks before conception until eight weeks after conception to prevent neural tube defects (van der Pal-de Bruin et al., 2000; McGovern et al., 1997). Predictors for this non-compliancy are, of course, mainly pointing towards unplanned pregnancies, but this advised folic acid intake in a Dutch study from 2005 still showed only a compliance rate of 61% in the planned pregnancies (de Walle and de Jong-van den Berg, 2008). Moreover, compliance rates as low as 31% were observed in less educated women in their study. Notably; educational level is a major contributor to socioeconomic status and particularly women with a low socioeconomic status are at increased risk of PE (Silva et al., 2008). Next to the therapy compliance, there are also other parameters which can influence the results of our CEA, such as indirect costs of the test such as technician's salary and other overheads, willingness of the pregnant women to get tested and of the clinicians to use the test and the implementability of a routine first trimester test. In conclusion, not all uncertainties can be taken into account in a sensitivity analysis, since there will always be some structural assumptions and underlying parameters that will influence a model. Nevertheless, the results of this study showed that a test strategy to screen for PT PE in the first trimester is potentially cost-effective in the Dutch setting.

Ethics approval and consent to participate

Not applicable.

Funding

Not applicable.

CRediT authorship contribution statement

Rik H.J. Beernink and Antoinette D.I. van Asselt analyzed and interpreted the cost-effectiveness data. Rik H.J. Beernink, Thomas I.F.H. Cremers and Antoinette D.I. van Asselt were a major contributor in writing the manuscript. Thomas I.F.H. Cremers devised the conceptual idea. Sicco A. Scherjon was responsible for the clinical data and interpretation. Antoinette D.I. van Asselt supervised the project. All authors read and approved the final manuscript.

Declaration of Competing Interest

All authors have approved the manuscript and agree with this submission. The author Rik Beernink and Thomas Cremers have a conflict of interest, since Rik is employed by IQ Products and Thomas is shareholder of IQ Products. The remaining authors report no conflict of interest.

Acknowledgements

Not applicable.

Consent for publication

All authors approved the final manuscript.

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