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ORIGINAL ARTICLE *Early pregnancy*

Predicting the likelihood of successful medical treatment of early pregnancy loss: development and internal validation of a clinical prediction model

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STUDY QUESTION: What are clinical predictors for successful medical treatment in case of early pregnancy loss (EPL)?

SUMMARY ANSWER: Use of mifepristone, BMI, number of previous uterine aspirations and the presence of minor clinical symptoms (slight vaginal bleeding or some abdominal cramps) at treatment start are predictors for successful medical treatment in case of EPL.

WHAT IS KNOWN ALREADY: Success rates of medical treatment for EPL vary strongly, between but also within different treatment regimens. Up until now, although some predictors have been identified, no clinical prediction model has been developed yet.

STUDY DESIGN, SIZE, DURATION: Secondary analysis of a multicentre randomized controlled trial in 17 Dutch hospitals, executed between 28 June 2018 and 8 January 2020.

PARTICIPANTS/MATERIALS, SETTING, METHODS: Women with a non-viable pregnancy between 6 and 14 weeks of gestational age, who opted for medical treatment after a minimum of 1 week of unsuccessful expectant management. Potential predictors for successful medical treatment of EPL were chosen based on literature and expert opinions. We internally validated the prediction model using bootstrapping techniques.

MAIN RESULTS AND THE ROLE OF CHANCE: 237 out of 344 women had a successful medical EPL treatment (68.9%). The model includes the following variables: use of mifepristone, BMI, number of previous uterine aspirations and the presence of minor clinical symptoms (slight vaginal bleeding or some abdominal cramps) at treatment start. The model shows a moderate capacity to discriminate between success and failure of treatment, with an AUC of 67.6% (95% CI = 64.9–70.3%). The model had a good fit comparing predicted to observed probabilities of success but might underestimate treatment success in women with a predicted probability of success of ~70%.

LIMITATIONS, REASONS FOR CAUTION: The vast majority (90.4%) of women were Caucasian, potentially leading to less optimal model performance in a non-Caucasian population. Limitations of our model are that we have not yet been able to externally validate its performance and clinical impact, and the moderate accuracy of the prediction model of 0.67.

WIDER IMPLICATIONS OF THE FINDINGS: We developed a prediction model, aimed to improve and personalize counselling for medical treatment of EPL by providing a woman with her individual chance of complete evacuation.

STUDY FUNDING/COMPETING INTEREST(S): The Triple M Trial, upon which this secondary analysis was performed, was funded by the Healthcare Insurers Innovation Foundation (project number 3080 B15-191).

TRIAL REGISTRATION NUMBER: Clinicaltrials.gov: NCT03212352.

Key words: personalized medicine / prediction model / early pregnancy loss / misoprostol / mifepristone

Introduction

Early pregnancy loss (EPL) is defined as a non-viable first trimester intrauterine pregnancy, in which there may be an anembryonic gestation or embryonic death (Neilson *et al.*, 2009; NICE guideline, 2019). It is the most common complication in early pregnancy, with a reported incidence varying from 10% to 28% of pregnancies (Ammon Avalos *et al.*, 2012; Buck Louis *et al.*, 2016). The estimated annual number of pregnancies worldwide is 227 million, meaning every year millions of women will seek treatment for EPL.

When faced with EPL, women can opt for either expectant, surgical or medical management. Expectant management for at least 1 week, leading to a spontaneous miscarriage in ~50% of women, is common practice in North-Western Europe, and also advised in the NICE (National Institute for Care and Health Excellence) guideline (NICE guideline, 2019). Although very effective in reaching complete evacuation (>95% success rate), surgical management bears several risks of early and late complications, such as intrauterine adhesion formation and increased risk of premature delivery in subsequent pregnancies, and comes with higher costs (You and Chung, 2005; Lemmers *et al.*, 2016). Until recently, in case of medical treatment, misoprostol monotherapy has been advised most often (ACOG: The American College of Obstetricians and Gynaecologists, 2019; NICE guideline, 2019). Reported success rates of misoprostol treatment vary strongly from 54% after at least 1 week of expectant management (Graziosi *et al.*, 2004; Van Den Berg *et al.*, 2014), up to 84% if prompt treatment is applied (Zhang *et al.*, 2005). Alongside two other recent studies, our Triple M Trial, a multicentre randomized placebo-controlled trial, shows that pre-treatment with mifepristone increases the success rate of medical treatment, after at least 1 week of unsuccessful expectant management from 58% to almost 80% (Schreiber *et al.*, 2018; Chu *et al.*, 2020; Hamel *et al.*, 2021).

For the individual woman with EPL, the probability of successful treatment (complete evacuation of the products of conception) has the greatest impact on her preferred treatment (Hentzen et al., 2017). Already in 2006, Graziosi *et al.* (2006) described that the majority of women with EPL choose medical treatment if complete evacuation rates exceed 65%. Additionally, it has been shown that women report higher satisfaction when treated according to their preferences (Wallace *et al.*, 2010). Thus, a tool providing an individual her probability of treatment success with medical management, could be useful in the shared decision-making process, for applying either medical or surgical management in case of EPL.

Although some clinical predictors appear to predict treatment success of medical treatment of EPL, no prediction models exist to date (Schreiber *et al.*, 2015; Fernlund *et al.*, 2020; Sonalkar *et al.*, 2020). With this study, we aimed to develop and internally validate a prediction model for successful medical treatment of EPL, after a minimum of 1 week of unsuccessful expectant management.

Materials and methods

Setting

This study is a secondary analysis of data from a multicentre randomized trial of medical treatment for EPL after a minimum of 1 week of unsuccessful expectant management, the Triple M Trial (Hamel *et al.*, 2021). In brief, 351 women participated in a multicentre, randomized, placebo-controlled, double-blinded trial comparing the effectiveness of pre-treatment with mifepristone 600 mg or placebo prior to misoprostol 36–48 h later as treatment for EPL, after a minimum of 1 week of unsuccessful expectant management. The final study cohort consisted of 344 patients, 172 in both treatment groups.

Women aged 16 years or older, who were diagnosed with a non-viable intrauterine pregnancy between 6 and 14 weeks of gestational age were eligible for inclusion. Women who were clinically unfit for medical management were excluded, as well as women with a miscarriage in progress (defined as increasing or heavy vaginal bleeding and/or abdominal cramping) or with an incomplete miscarriage. The primary outcome was complete evacuation, defined as loss of the gestational sac and an endometrial thickness of <15 mm, at the latest 6–8 weeks after treatment start.

Ethical approval

For the development of this prediction model, no separate ethical approval was required. Approval for the Triple M Trial, upon which this model was based, was obtained from the regional medical-ethical commission (Commissie Mensgebonden Onderzoek Arnhem-Nijmegen), file number NL 62449.091.17. The Triple M Trial was also registered at Clinicaltrials.gov: NCT03212352; Trialregister.nl: Trial NL 6366; and EudraCT: number 2017-002694-19.

Selection of potential predictors

Preselection of potential predictors was based on clinical reasoning, univariate analysis and current literature. As medical abortion may be similar to EPL treatment in some respects, both literature about predictors for successful EPL treatment, as well as predictors for successful early medical abortion of vital pregnancy, were investigated.

In 2006, Creinin *et al.* (2006) found that lower abdominal pain or vaginal bleeding within the last 24 hours of treatment start, Rh-negative blood type, and nulliparity were predictive of overall success in misoprostol treatment for EPL. Recently, Sonalkar *et al.* (2020) aimed to identify clinical predictors of treatment success in women promptly treated with sequential mifepristone and misoprostol or misoprostol alone in case of EPL. Apart from the use of mifepristone, and being a non-smoker, no significant clinical predictors of treatment success were found in their study (Sonalkar *et al.*, 2020). Most recently, Fernlund *et al.* (2020) investigated predictors of complete miscarriage after expectant or misoprostol treatment. No variable predicting success of misoprostol treatment was found. Studies into predicting successful medical termination of vital pregnancy found both maternal and gestational age, parity and previous termination to be relevant predictors (Bartley *et al.*, 2000; Ashok *et al.*, 2002; Reeves *et al.*, 2016).

Predictors found to be relevant in predicting successful uterine evacuation from previous research are shown in Table I.

We performed a univariable analysis to identify potential predictors not yet selected in previous research or by clinical reasoning (data shown in Table II). Data of all predictors were obtained from the case report form (CRF) used in the Triple M Trial.

Clinically important variables, and variables that show significance ($P < 0.25$) in univariable analysis, were included for multivariable analysis and led to the final set of candidate predictors for multivariable

Table I Possible predictors identified in previous research.

Author	Situation	Predicting successful treatment	Predicting treatment failure
Reeves et al. (2016)	Medical termination of vital pregnancy	≥5 prior deliveries, gestational age ≥8 weeks	Age ≤20 years
Ashok et al. (2002)	Medical termination of vital pregnancy	–	Previous termination of a vital pregnancy
Bartley et al. (2000)	Medical termination of vital pregnancy	Gestational age, parity	–
Creinin et al. (2006)	Early pregnancy loss	Active bleeding, nulliparity	–
Sonalkar et al. (2020)	Early pregnancy loss	Mifepristone pretreatment, smoking	–
Fernlund et al. (2020)	Early pregnancy loss	–	–

Table II Univariate analysis of possible predictors, not yet included from previous research or clinical reasoning.

Possible predictor	*P*-value	Chi-square	OR
Ethnicity	0.667	5.823	–
Previous EPL	0.992	0.000	1.002 (0.609–1.650)
Previous medical EPL treatment	0.545	1.214	0.923 (0.789–1.080)
Diagnosis	**0.191**	1.003	1.294 (0.781–2.146)
Previous uterine aspiration	**0.206**	1.598	0.608 (0.279–1.323)

EPL, early pregnancy loss; OR, odds ratio.
The boldface values are the predictors that show signficance in univariable analysis, as the threshold for significance is $P < 0.25$.

analyses (Hosmer et al., 2013):use of mifepristone, gravidity, parity, gestational age, maternal age, BMI, diagnosis at inclusion (foetal demise or empty gestational sac), number of previous uterine aspirations and presence of minor clinical symptoms (slight vaginal bleeding or some abdominal cramps) at treatment start.

Sample size

Our sample size consisted of 344 women, participating in the Triple M trial and finally included in the intention-to-treat analysis. In this analysis, the predefined event was unsuccessful treatment, as this is the smaller number of binary outcomes, occurring 107 times. As at least 10 events are recommended for each potential predictor, to reduce bias in regression coefficients (Peduzzi et al., 1996), a model was developed from a maximum of 10 potential predictors.

Data collection

All data used to develop the prediction model were acquired from participants of the Triple M Trial. Data were gathered through custom CRFs at all participating sites, completed by trained research nurses or medical doctors.

Data quality and missing data

Data were checked for completeness and inconsistencies, and if any were found, these were checked with the hospital concerned. Data that were not registered on either the CRF or in the patients' chart were imputed with multiple imputation, with the number of imputations set to five, in order to limit bias in the results and loss of precision of the model (Donders et al., 2006; Steyerberg, 2009). To check whether results had changed significantly, the outcomes of the imputed data set were compared with complete case analysis.

Model development

In all five imputed data sets all potential predictors were introduced in a multivariable logistic regression model, with treatment success as outcome variable. Backward stepwise conditional selection was used to select the number of predictors in the model. A *P*-value of 0.20 was used as recommended by prediction modelling guidelines, to ensure a more liberal inclusion of potential predictors (Harrell, 2001). As more recently the Akaike Information Criterion is advised to be used in backward selection, corresponding with a *P*-value of 0.157, leading to a stricter inclusion of predictors (Moons et al., 2015), we also modelled according to these more stringent criteria. After applying both conditions separately, no differences in variable selections were found. Predictors were only included in the final model if they remained in the model in three or more of the five imputed data sets. Finally, the results of these five models were combined, leading to a single prediction model.

Internal validation

To reduce the risk of an over-fitted model, which performs well for the data it was derived upon, but performs considerably worse in future patients, internal validation was applied by bootstrapping. Here, 1000 bootstrap samples, of the same size as the original sample, were drawn with replacement from the original data upon which the definitive model is based. This internal validation procedure provides an indication of uncertainty, as it reflects the drawing of this many samples from the underlying population. The model can then be adjusted using the bootstrap shrinkage factor, to ensure predictions to be more fitting, leading to better performance of the model in future patients.

Performance of the model

After internal validation, the performance of the model was assessed. The ability of the model to discriminate between treatment success and treatment failure was quantified as AUC. The agreement between predicted probabilities and observed outcome frequencies was displayed in a bar chart and calibration curve (Coppus et al., 2009). Thereafter, a clinical decision tool in the form of a score chart, also displayed as a nomogram, was developed, with corresponding success

chances for the whole range of scores. All statistical analyses were performed using SPSS 26.0 and R version 4.0.2.

Results

Patient population

In the primary analysis of our randomized controlled trial, a total of 344 women were included in the intention-to-treat analysis, and subsequently eligible for developing this model. A flowchart of inclusion is shown in Fig. 1. Baseline characteristics and missing values are presented in Table III. The overall complete evacuation rate was 68.9%, differing significantly between the treatment and control group (79.1% vs 58.7% respectively, $P < 0.0001$).

Model development and internal validation

For each potential predictor, the number of missing values is shown in Table III. Data were found to be missing most often for BMI (18.0%), all other variables had <2% missing data. Missing data were missing completely at random (MCAR). This was tested with Little's MCAR test, which showed a significance value of 0.722, meaning the null hypotheses that data are indeed MCAR, should be retained. After multiple imputation, data from all 344 women were available for multivariable modelling.

Subsequently, all candidate predictors were entered in the model, resulting in four predictors that met the predefined selection criteria. These were: use of mifepristone, BMI, number of previous aspirations and minor clinical symptoms at treatment start. These four variables were combined into one model. BMI and the number of previous uterine aspirations are continuous variables, pre-treatment with mifepristone and presence of minor clinical symptoms at treatment start are dichotomous. To ensure data imputation did not lead to completely different results, we compared outcomes of the imputed data with outcomes of complete cases only. In this analysis, we found similar results for both datasets, meaning the same predictors met the selection criteria and were thus combined into the model.

In Table IV, both the original regression coefficients and the regression coefficients adjusted after internal validation are shown. The bootstrap validation yielded a shrinkage factor of 0.99, which was used to multiply the regression coefficients. The intercept was also re-estimated, leading to the final predictive equation to estimate the individual probability of successful medical treatment in case of EPL: $P_{(success)} = 100\% * 1/\{1 + \exp[-(-1.563 + 0.991 * \text{Treatment} + 0.077 * \text{BMI} + 0.853 * \text{physical complaints present at randomization} - 0.501 * \text{number of previous uterine aspirations})]\}$.

Filling out this equation leads to the highest predicted chance of success (96.9%) in a patient with optimal characteristics in our study population; pre-treatment with mifepristone, highest BMI in our study population (41.3 kg/m^2), minor clinical symptoms at randomization and no previous uterine aspirations. If all relevant characteristics were the least optimal this led to the lowest chance of success in our study population, which is 15.2% (treatment with misoprostol only, lowest BMI in our study population (17.5 kg/m^2), no physical complaints at

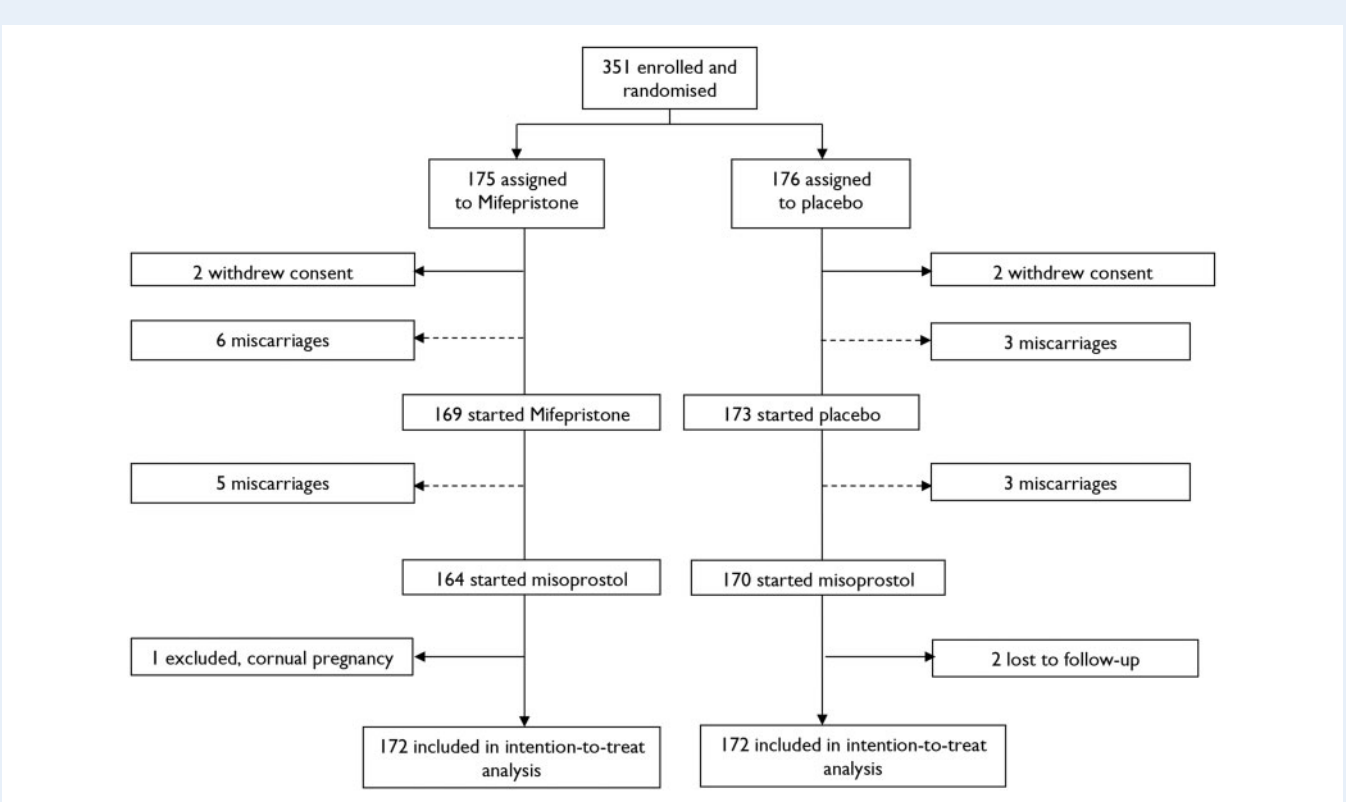

Figure 1. Trial profile. - - - - ▶ = included in intention-to-treat analysis. ——▶ = excluded from intention-to-treat analysis.

Table III Basic characteristics and missing values.

Characteristic	Missing values N (%)	Participants (N = 344)
Age in years, mean (SD)	0 (0)	32.82 (4.34)
BMI, mean (SD)	62 (18.0)	24.40 (4.16)
Race or ethnic group, N (%)	8 (2.3)	
Caucasian		311 (90.4)
Middle Eastern		13 (3.8)
Asian		5 (1.5)
Other		7 (2.0)
Gravidity, N (%)	0 (0)	
1		135 (39.2)
2		116 (33.7)
≥3		93 (27.0)
Parity, N (%)	0 (0)	
0		177 (51.5)
1		134 (39.0)
≥2		33 (9.6)
Gestational age based on amenorrhoea in days, mean (SD)	6 (1.7)	70.66 (11.30)
Gestational age in weeks, N (%)		
≤7		26 (7.6)
8		55 (16.0)
9		89 (25.9)
10		74 (21.5)
11		54 (15.7)
12 or more		40 (11.6)
Ultrasonographic diagnosis, N (%)	0 (0)	
Embryo without cardiac activity		238 (69.2)
Anembryonic gestation		106 (30.8)
Number of prior aspirations, N (%)	2 (0.6)	
0		313 (91.0)
1		23 (6.7)
2		5(1.5)
3		1 (0.3)
Physical complaints at randomization, N (%)	3 (0.9%)	
Yes		47 (13.7)
No		294 (85.5)
Treatment regimen, N (%)	0 (0%)	
Mifepristone and misoprostol		172 (50.0)
Placebo and misoprostol		172 (50.0)

randomization and three previous uterine aspirations (highest number in our study population)).

Performance of the model

Figure 2 shows the receiver operating characteristic curve of the final prediction model, and its optimism corrected AUC. The (optimism corrected) AUC was found to be 67.6% (95% CI = 64.9–70.3%). Predicted probabilities ranged from 30.6% to 97.1% with a mean of 68.9% (SD 13.8%).

Calibration of the model is shown in Figs 3 and 4, with Fig. 3 displaying mean predicted probabilities versus mean observed probabilities of complete evacuation, divided equally over eight groups. Each group represents a range of 12.5% of all predicted probabilities (i.e. Group 1 lowest 12.5% of probabilities, Group 8 highest 12.5% of probabilities, etc.). The calibration curve of the model is displayed in Fig. 4, showing an overall good calibration with a slope only slightly <1 and an intercept just above 0. In both figures, it is clear that the model is the least accurate in the group with a mean predicted probability of success around 0.7, corresponding to a chance of 70% (Group 4 in Fig. 3). In this group, the predicted probability of success was clearly lower than observed. Additionally, however, within the presented model, we were not yet able to select the small subset of women with the highest probability of treatment failure, for whom a primary vacuum aspiration might be a better treatment option.

To enhance the use of our model in clinical practice, we developed a decision instrument in the form of a score chart, which is shown in Table V, along with the chances of success associated with each score in the possible score range in Table VI. A more visual representation of this score chart is shown in the nomogram in Fig. 5, in which each factor had a score on the point scale, which can be determined by drawing a straight line from the factor scale to the point scale. The estimated chance of success can be calculated by adding all points to generate a point total, locating this score on the total point scale and subsequently the corresponding chance of success.

Discussion

Main findings

A prediction model for successful medical treatment of EPL after at least 1 week of unsuccessful expectant management was developed and internally validated, following recent methodological guidelines in prognostic modelling (Harrell, 2001; Steyerberg, 2009; Steyerberg *et al.*, 2013). Four variables could be included in the final model; pretreatment with mifepristone, BMI, number of prior curettages and presence or absence of minor clinical symptoms at randomization. The prediction model we developed is reasonably discriminative and accurate, especially in women with a predicted probability of success of 40% or higher, which applies to the vast majority of women (98.1%).

Strengths and limitations

A strength of this prediction model is that it is based on a sufficiently powered double-blinded randomized controlled trial, providing a sufficient amount of valid data. Additionally, there were only very few, and all randomly missing data. To ensure the small amount of missing data did not influence our model we compared outcomes for both the imputed and complete case datasets, which showed similar results.

The inclusion criteria of the Triple M trial were defined in such a way that a representative study population with EPL after a minimum of 1 week of unsuccessful expectant management was acquired. An

Table IV Prediction model for successful medical treatment in case of early pregnancy loss, with regression coefficients and odds ratios before and after internal validation.

Variable	Crude regression coefficient	OR (95% CI)	Adjusted regression coefficient	OR (95% CI)
Intercept	−1.584	0.205 (0.103–0.408)	−1.563	0.210 (0.105–0.417)
Mifepristone pre-treatment (yes/no)	1.001	2.720 (2.185–3.385)	0.991	2.694 (2.164–3.353)
BMI	0.078	1.081 (1.0510–1.112)	0.077	1.080 (1.050–1.111)
Minor clinical symptoms present at treatment start (yes/no)	0.862	2.367 (1.685–3.325)	0.853	2.347 (1.670–3.297)
Number of previous uterine aspirations	−0.507	0.6026 (0.4661–0.779)	−0.501	0.606 (0.469–0.783)

OR, odds ratio.

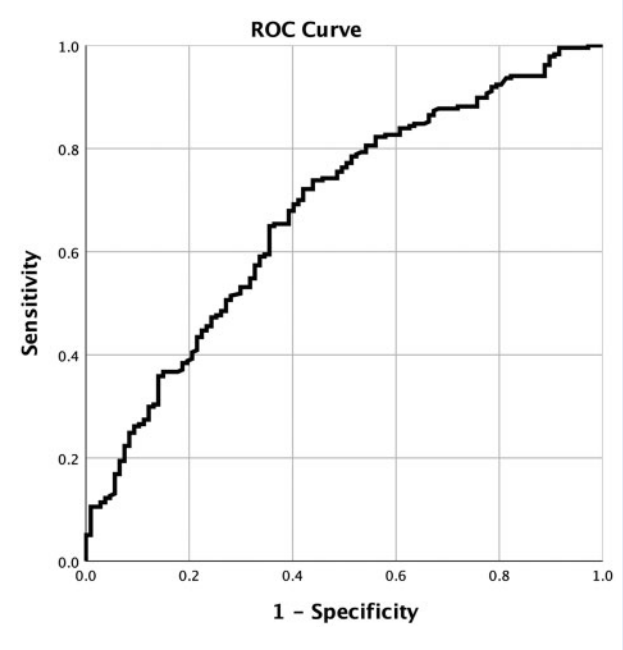

Figure 2. Receiver operating characteristic curve of the prediction model. Area under the curve = 67.6% (95% CI = 64.9–70.3%), indicating reasonable discriminative performance.

expectant policy, leading to spontaneous miscarriage in ~50% of women with EPL is common practice in North-Western Europe (NICE guideline, 2019; Nederlandse Vereniging van Obstetrie en Gynaecologie, 2020), which may lead to a selected, not yet spontaneously aborted, group of women with more 'persistent' products of conception. This may be an explanation for the fact that we found more predictors than Sonalkar *et al.* (2020), applying prompt treatment after EPL diagnosis. Additionally, the average gestational age in the trial of Sonalkar *et al.* (2020) was 7 weeks, compared to 10 weeks in the Triple M trial, which makes the two study populations difficult to compare.

A limitation of our data might be the fact that the vast majority (90.4%) of women were Caucasian, potentially leading to less optimal model performance in a non-Caucasian population. Although ethnicity is not assumed to have an effect on treatment outcome for EPL, we cannot refute this.

The presented model has reasonable discriminative capacity with an AUC of 67.6%, with a good calibration as shown by the calibration curve. Only in the group of women with a predicted probability (or chance of success) around 0.7 (or 70%, respectively), the model is less accurate, predicting lower chances than those observed.

This model can be a useful tool for healthcare providers to improve counselling. For the individual patient, receiving her individual chance of complete evacuation, is very relevant. For example, the difference between a 60% or 90% chance of success will influence expectations and experiences with the chosen treatment, and might make a patient opt for medical instead of surgical treatment, or vice versa. However, using only the presented model we were not yet able to select the small subset of women with the highest probability of treatment failure, for whom a primary vacuum aspiration would possibly be a better treatment option. This might be due to the fact that these low chances of success are rare. Individual patient data meta-analyses of the performed studies on pre-treatment with mifepristone in EPL, in which pooled data from multiple studies are combined and analysed might help to increase predictive power (Broeze *et al.*, 2009).

Another limitation of our prediction model is of course, which we have not yet been able to assess its external validity and clinical impact in a future population.

Interpretation

This is the first prediction model based on clinical predictors for successful medical treatment of EPL. Recently, Sonalkar *et al.* (2020) aiming to identify clinical predictors of prompt treatment success in case of EPL found non-smoking and also pre-treatment with mifepristone significant, but an actual prediction model was not constructed (Sonalkar *et al.*, 2020). Unfortunately, data regarding smoking of participants was not available in our study. Whether mifepristone pre-treatment was applied or not is also a strong predictor in the presented model. Of other predictors, only the presence of minor clinical symptoms (slight vaginal bleeding or some abdominal cramps) might be compared to the predictor 'active bleeding' of Sonalkar *et al.* (2020). The fact that mifepristone use is a significant predictor of treatment success, underlines the importance of incorporation of pre-

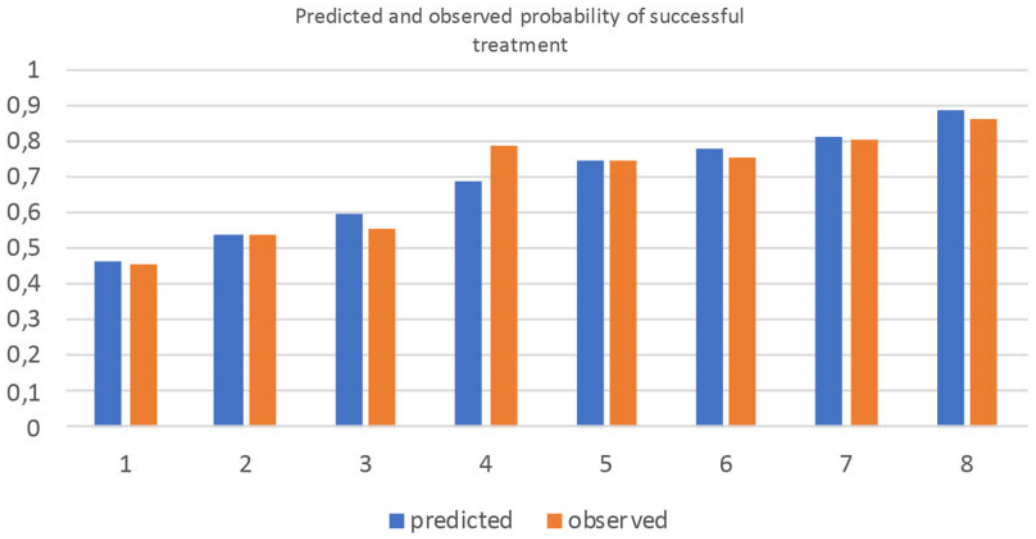

Figure 3. Predicted and observed probabilities of successful treatment per group of 215 predictions. Each group represents a range of 12.5% of all predicted probabilities (i.e. Group 1 lowest 12.5% of probabilities, Group 8 highest 12.5% of probabilities).

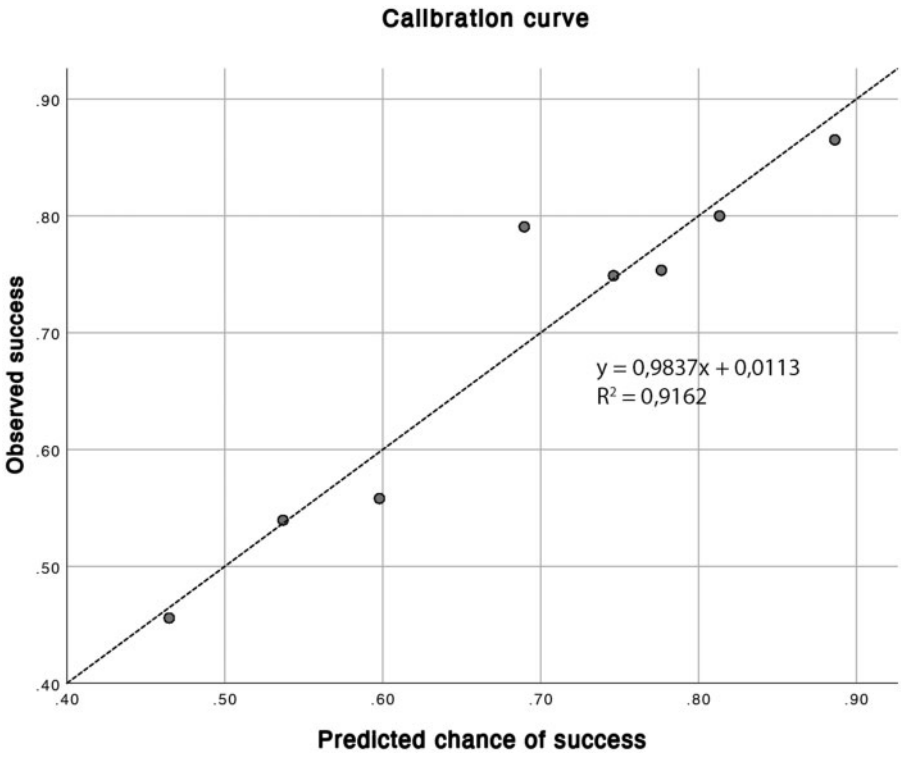

Figure 4. Calibration curve of prediction model for successful medical treatment of early pregnancy loss. Points show predicted and observed success rates for the eight groups shown in Fig. 3.

Table V Score chart for successful medical treatment in case of early pregnancy loss.

Predictor	Category	Points
BMI (kg/m^2)	≤18.5	1
	18.6–24.9	0
	25.0–29.9	−1
	≥30	−2
Minor clinical symptoms at treatment start	Yes	0
	No	2
Mifepristone pre-treatment	Yes	0
	No	2
Number of prior curettages	0	0
	1	1
	2	2
	3	3

Table VI Chance of success corresponding with scores from the score chart.*

Points	Chance of success
−2	0.899
−1	0.843
0	0.765
1	0.664
2	0.545
3	0.420
4	0.305
5	0.210
6	0.139
7	0.089
8	0.056

*See Table V.

treatment with mifepristone in case of EPL in current guidelines, whether or not after a period of unsuccessful expectant management. Furthermore, this is the only predictor which can be altered directly at the moment of consultation, in contrast to pre-existing predictors. It should however be noted that even with applying mifepristone pre-treatment patients' probability of success can still lie within the lower values, underlining the relevance of the other predictors on this model.

The finding that an increasing number of previous uterine aspirations is a predictor for unsuccessful treatment can indicate several points. Firstly, women who underwent surgical evacuation in any previous pregnancy might have already been unsuccessful in earlier attempts with medical treatment, leading to secondary uterine aspirations. Secondly, as it is known that cervical dilation can lead to damage and scarring of the cervical tissue, this may prevent cervical weakening with medical treatment in a next EPL, leading to lower chances of complete evacuation.

Our prediction model includes BMI as one of its predictors, with increasing BMI leading to a higher chance of complete evacuation. Previous studies found a relationship between obesity and the risk of EPL, but not between BMI and the need for surgical intervention in case of medical abortion (Lashen, 2004; Strafford *et al.*, 2009). However, in both studies, a cut-off value of 30 kg/m^2 defining obesity was used. Since in the Triple M Trial only 29 women had a BMI of 30 or higher, it is difficult to compare these findings to our study population. First trimester serum progesterone levels have been found to be significantly lower in obese women (Maliqueo *et al.*, 2017). As progesterone is essential in early pregnancy, a possible explanation for the correlation between increasing BMI and treatment success might be found in these lower progesterone levels. Medical treatment with prostaglandins may be more successful in the case of relatively low progesterone levels and even more successful when pre-treated with the progesterone antagonist mifepristone.

The presence of minor clinical symptoms, such as slight vaginal bleeding or some abdominal cramps, was also found to be a predictor for complete evacuation in this study. This may be explained by the fact that abdominal pain was also included as a clinical symptom, which may imply a started process of cervical ripening, contrary to Sonalkar *et al.* (2020) who only recorded vaginal bleeding. Although we excluded women with miscarriage in progress from participating in the study, the presence of even minor clinical symptoms might imply that spontaneous miscarriage is imminent. Therefore, it makes sense that this is a significant predictor of complete evacuation, i.e. complete miscarriage.

The performance of a solid model for the prediction of successful medical treatment of EPL might be further enhanced by the use of so-called biomarkers, as metallopeptidase domain 12 (ADAM12, influencing cell–cell and cell–matrix interactions) and hCG levels have been shown to be associated with treatment success (Schreiber *et al.*, 2015). However, it is highly preferable that only easy accessible, and affordable, clinical predictors are used allowing 'on the spot' counselling, ensuring the application of the model also in low-income countries.

As evidence-based counselling followed by shared decision-making, and applying a patients' preferred treatment regimen, have been found to lead to better outcomes (Wieringa-De Waard *et al.*, 2002; Coulter and Collins, 2011), this individualized, patient-directed prediction model, using simple parameters may contribute to improving treatment outcomes worldwide.

Future research should consist of the external validation of this model, prior to implementation in clinical practice.

Conclusion

We developed and internally validated a prediction model, predicting successful medical treatment in case of EPL after a minimum of 1 week of unsuccessful expectant management. Pre-treatment with mifepristone (yes/no), BMI, number of previous uterine aspirations and the presence of minor clinical symptoms (yes/no) at treatment start were found to be the four relevant predictors, of which only the use of mifepristone can be altered during consultation. As our

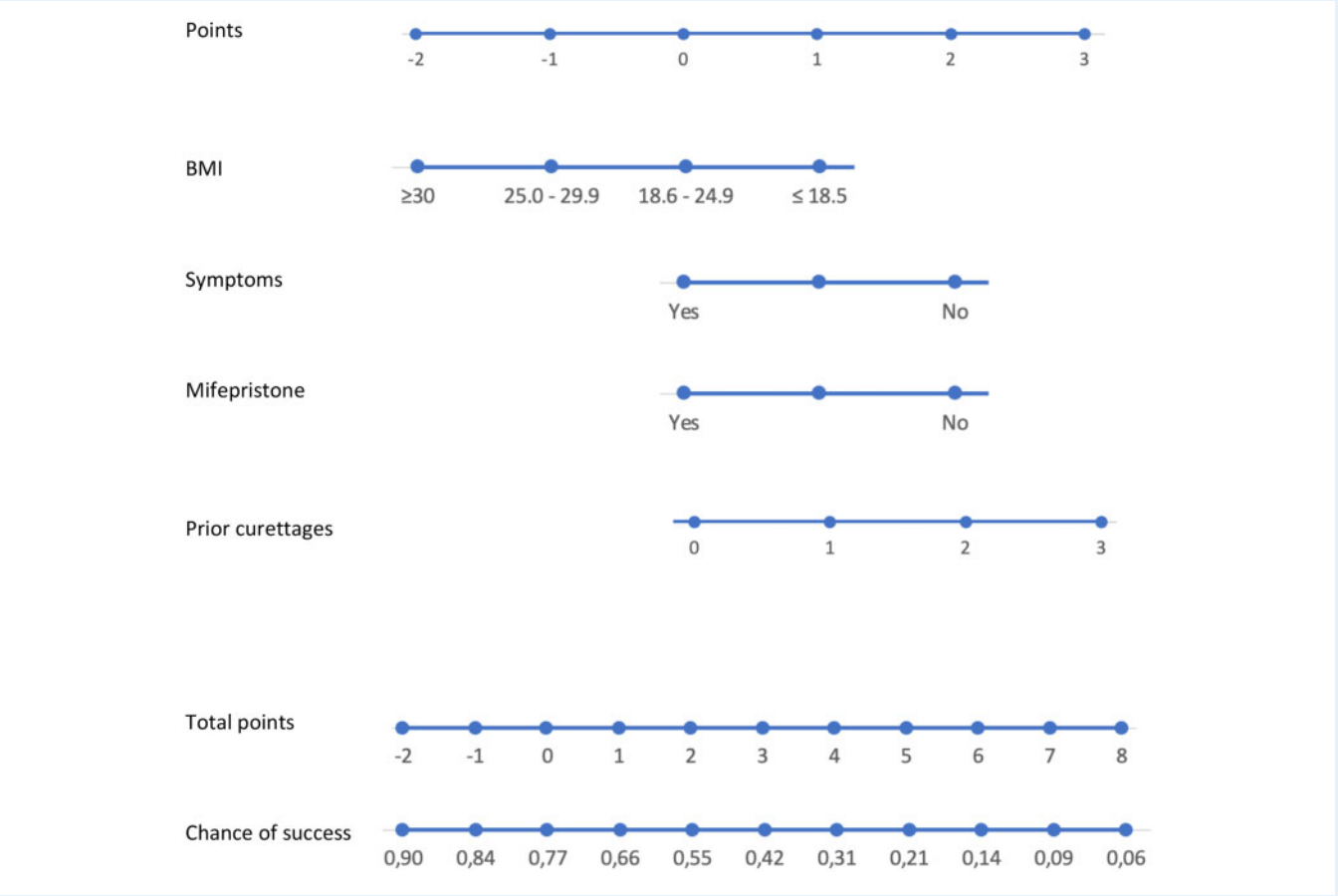

Figure 5. A nomogram for prediction of the chance of successful medical treatment in case of early pregnancy loss. Each factor (BMI, symptoms, mifepristone, prior curettages) has a score on the point scale, which can be determined by drawing a vertical line from the factor scale to the point scale. The estimated chance of success is calculated by adding all points to generate a point total, locating this score on the total point scale and subsequently the corresponding chance of success.

model and derived clinical prediction rule can provide more clarity in a woman's individual chance of successful medical treatment of EPL, it may optimize treatment outcomes, as patients can make a better-informed choice. External validation is required prior to clinical implementation.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Authors' roles

C.C.H. was the coordinating investigator of the Triple M Trial and was responsible for data collection. F.P.H.A.V., M.P.L.M.S. and S.F.P.J.C. contributed to the protocol and design of the trial. C.C.H. and P.V. analysed the data. F.P.H.A.V., M.P.L.M.S., S.F.P.J.C., D.D.M.B., P.V. and C.C.H. contributed to the interpretation of the results. C.C.H. drafted the article, all other authors provided critical input and editing. All authors gave approval for the submission of the final manuscript.

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Conflict of interest

The authors declare that they have no conflicts of interest.

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