A multivariable model to guide the decision for pessary placement to prevent preterm birth in women with a multiple pregnancy: a secondary analysis of the ProTWIN trial

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ABSTRACT

OBJECTIVE: The ProTWIN Trial (NTR1858) showed that in women with a multiple pregnancy and a cervical length less than the 25th percentile (38*mm*), prophylactic use of a cervical pessary reduced the risk of adverse perinatal outcome. We investigated whether other maternal or pregnancy characteristics collected at baseline can improve identification of women with the most probable benefit from pessary placement.

METHODS: ProTWIN is a multicenter randomized trial in which 808 women with a multiple pregnancy were assigned to pessary or control. Using this data we developed a multivariable logistic model comprising treatment, cervical length, chorionicity, pregnancy history and number of fetuses and the interaction of these variables with treatment as predictors of adverse perinatal outcome.

RESULTS: Short cervix, monochorionicity and nulliparity were predictive factors for a benefit from pessary insertion. History of previous preterm birth and triplet pregnancy were predictive factors of possible harm from pessary. The model identified 35% of women as benefiting (95% CI: 32% to 39%), which is 10% more than using cervical length only (25%) for pessary decisions. The model had acceptable calibration. We estimated that using the model to guide the choice of pessary would reduce the risk of adverse perinatal outcomes significantly from 13.5% when no pessary is inserted to 8.1% (absolute risk reduction 5.4%, 95% CI: 2.1% to 8.6%).

CONCLUSIONS: We developed and internally validated a multivariable treatment selection rule, with cervical length, chorionicity, pregnancy history and number of fetuses. If externally validated, it can be used to identify women with a twin pregnancy who benefit from a pessary, and therefore a reduction in adverse perinatal outcomes in twin pregnancies can be anticipated.

INTRODUCTION

Preterm birth - birth before 37 weeks' gestation - is worldwide the second most common cause of death in children under 5 years and is responsible for about 35% of deaths in the first 4 weeks of life[1]. Women with a multiple pregnancy are more prone to a preterm delivery and its complications[2]. There have been many attempts to reduce the risk of preterm birth in these women by prophylactic use of vaginal progesterone, 17α-hydroxyprogesterone caproate, cervical cerclage, and cervical pessary[3-10].

Recently, our group reported the ProTWIN trial, in which women with a multiple pregnancy between 12 and 20 weeks' gestation were randomly allocated to either a pessary or control group. Overall, cervical pessary did not effectively reduce the risk of adverse perinatal outcome or preterm birth in the ProTWIN trial. Yet in a pre-specified subgroup analysis inserting a pessary was shown to significantly reduce the risk of adverse perinatal outcome and very preterm delivery in women with a cervix shorter than 38 mm. The threshold for defining a short cervix was obtained from the distribution of cervical length in the study participants: 25% of women had cervix shorter that 38 mm at study entry[4].

Although the definition of short cervix in the study was pre-specified as the 25th percentile of the distribution of the cervical length in the study group, the question is whether this cut-point is the optimal one for identifying women who could benefit from inserting a pessary to prevent preterm birth. Furthermore, it is conceivable that not just cervical length but also other patient characteristics could be associated with the benefit from using a cervical pessary. There is mounting evidence that the effectiveness and safety of medical interventions vary across patient populations and many patient characteristics can potentially influence the response to treatment. Among these

characteristics are factors which determine the baseline risk in the absence of treatment. Individuals who are at higher risk of complications, have a higher potential to benefit more from interventions[11, 12]. In the context of poor perinatal outcome and preterm birth in multiple pregnancies, several risk factors have been reported, such as parity[13], a previous preterm delivery[14], a monochorionic pregnancy[15] and a triplet pregnancy[16].

In a secondary analysis of the ProTWIN trial we performed an exploratory analysis with these risk factors, which had also been specified in the trial protocol. We aimed to investigate the potential and performance of these additional risk factors in the prediction of benefit from pessary insertion, and to evaluate whether combining them in a multivariable treatment selection model could potentially improve identification of women who benefit from a pessary.

MATERIALS AND METHODS

Study design and patients

We used data collected in the ProTWIN study (NTR1858), a multicenter open-label randomized controlled trial, conducted in 40 hospitals in The Netherlands[3, 4], in which 813 women with a multiple pregnancy between 12 and 20 weeks' gestation had been included (Figure 1). The study has been approved by the research ethics committee of the Academic Medical Centre in Amsterdam (MEC 09-107, NTR1858) and by the board of each participating hospital. All participants provided written informed consent. Participants were randomly allocated (1:1) to either a pessary or a control group. An obstetrician or sonographer measured cervical length between 16 and 22 weeks' gestation, either before or shortly after randomization. For women in the pessary group, pessary was inserted between 16 and 20 weeks' gestation and it was removed in the

36th week of gestation or before, in case of premature rupture of the membranes, active vaginal bleeding, other signs of preterm labor, or severe patient discomfort. Women in the control group did not receive the pessary, but received obstetrical care otherwise similar to those in the pessary group. Further details of the trial are presented elsewhere[4].

The primary outcome was a composite of the following adverse perinatal outcomes: stillbirth, periventricular leucomalacia, severe respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular haemorrhage, necrotising enterocolitis, proven sepsis, and neonatal death within 6 weeks after the expected term date, all as defined previously[17-21]. Time to delivery and preterm birth before 32 weeks were considered as secondary outcomes[7].

Potential treatment selection factors we evaluated were cervical length, chorionicity (monochorionic vs dichorionic), Obstetric history (nulliparous vs parous with no previous preterm birth vs parous with at least one previous preterm birth) and number of fetuses (twin vs triplet).

Statistical analysis

We explored the association between cervical length and benefit from pessary insertion by plotting the risk of adverse perinatal outcome as a non-parametric function of cervical length. We did so for the pessary and the control group separately, in Subpopulation Treatment Effect Pattern Plots (STEPP), as proposed by Lazar and colleagues[22].

To investigate the potential of the candidate variables for treatment selection, we built a series of logistic regression models, each including a single variable, a treatment

indicator (pessary vs control) and a variable by treatment interaction. Cervical length was modeled as a dichotomous variable (<38mm, ≥38mm) because the STEPP plot showed a non-linear association between cervical length and the extent of benefit from pessary. Pregnancy history was modeled as a single categorical variable with three levels: nulliparous, parous without previous preterm delivery and parous with previous preterm delivery. We assumed that pessary had an effect on adverse perinatal outcomes by influencing time to delivery. To corroborate the observed associations, we repeated the analyses for each variable with delivery before 32 week as the outcome.

We then developed a multivariable logistic regression model with all the variables and their interaction terms with treatment. Cervical length was missing in 24% of women. To increase the statistical power of the multivariable modeling and to lower the possibility of bias from a complete case analysis, we imputed missing values with Multiple Imputation by Chained Equations (MICE) approach ten times[23]. Model building and estimation of regression coefficients were performed in each imputation set separately. Estimates for the final multivariable model were obtained by combining the ten regression coefficients and their respective standard errors using Rubin's rule[24]. This technique takes into account the variability in results between the imputed complete datasets and adds uncertainty of the imputed data into the confidence intervals of parameter estimates. The details of the imputation technique are reported in the Online Supplement 1.

Model performance in risk prediction was assessed as discrimination and calibration. To correct for potential overfitting, we (internally) validated the model with bootstrapping techniques. To evaluate the performance of the multivariable model for treatment selection, we used the model to calculate the risk of adverse perinatal outcome without

pessary for each woman that had participated in the ProTWIN trial. We then used the model to calculate, for the same woman, the risk of an adverse perinatal outcome with a pessary. We then subtracted the risk of an adverse perinatal outcome with a pessary from the risk without pessary, to produce an absolute risk difference. This estimate can be regarded as an individual estimate of the treatment effect of pessary in the woman[25-27].

We first studied the distribution of the calculated risk differences in the trial participants. We assessed calibration of the calculated risk differences by comparing the average calculated risk difference with the observed difference in proportions of participants with adverse perinatal outcomes, in groups defined by the deciles of the distribution of risk differences[26].

Because a pessary is shown to be a relatively low cost intervention, without known major side effects, we assumed that any reduction in adverse perinatal outcome risk as a result of pessary placement would justify its use. Based on this assumption we classified women into those likely to benefit from using a pessary (a positive risk difference) and those not likely to benefit (a negative or zero risk difference). We then estimated the reduction in population rate of adverse perinatal outcome by using a strategy of model-based pessary insertion, compared to the following two strategies:

(1) Inserting pessary for no one

(2) Inserting pessary only in women with short cervix

These two estimates can be interpreted as the population benefit of using the model to guide the choice of a pessary, in terms of the expected reduction in the risk of adverse perinatal outcomes[25-27]. We estimated the above summary measures empirically. Confidence intervals for each estimate is obtained using the percentile bootstrap[26].

R for Windows (Version 3.0.1; R Foundation for Statistical Computing, Vienna, Austria) was used to perform all statistical analyses. Multiple imputation was done by package 'mice'[23] and evaluation of model performance for treatment selection and comparisons of the strategies were done by package 'TreatmentSelection'[26].

Role of the funding source

The funding sources had no roles in data collection, analysis, interpretation, report writing, or submission.

RESULTS

Table 1 summarizes the baseline characteristics of the trial participants. For 53 women (13%) in the pessary group at least one child had an adverse perinatal outcome, against 55 (14%) in the control group. The frequency of the individual components of the composite adverse perinatal outcome did not differ between the trial arms (Table 2). Median gestational age at delivery and maternal morbidity rates were comparable.

The relationship between cervical length and preventive effect of pessary

The 25th percentile of cervical length for the pre-specified subgroup analysis was 38 mm. In women with a cervical length of less than 38 mm, adverse perinatal outcomes were less frequently observed in the pessary group (12%) than in the control group (29%), while the corresponding percentages were comparable in women with cervical length 38 mm or more: 13% versus 10% (Table 3). This difference in the effect of pessary between women with a short and those with a long cervix was statistically significant (P for interaction 0.01).

Figure 2 presents the estimated association between the cervical length and the risk of adverse perinatal outcome. The graph suggests that, in this group of women, 38 mm would be an adequate cut-point for defining short cervix. In women with a cervical length of 38 mm or more the risk with and without a pessary is comparable, while the risk for those with a cervical length less than 38 mm is high without a pessary, and this risk can potentially be reduced by inserting a pessary.

The relationship between other variables and effect of pessary

Table 3 presents the association between the four investigated risk factors and adverse perinatal outcome in the pessary and control group. Monochorionic fetuses were at high risk of an adverse perinatal outcome in the control group (26%). This risk was lower in the pessary group, at 14% (OR 0.5; 95% CI: 0.2 to 0.97). In dichorionic pregnancies a pessary did not significantly change the risk of adverse perinatal outcome. The difference in the effect of pessary in monochorionic and dichorionic pregnancies was statistically significant (P for interaction 0.015).

We observed that in women with at least one previous preterm birth (n=55), the estimated risk of adverse perinatal outcome was significantly higher with a pessary (OR 11.2; 95% CI: 1.3 to 96.4), while in nulliparous women and multiparous women who had no previous preterm birth no significant preventive or adverse effect of pessary could be observed (P for interaction 0.009).

There were 18 women with a triplet pregnancy participating in the study. Two of the 9 women with a triplet pregnancy in the control group suffered adverse perinatal outcomes, compared to 4 of 9 women with a triplet pregnancy in the pessary group (OR 2.8; 95% CI: 0.4 to 21.7). The interaction with treatment was not statistically significant (P for interaction 0.30).

Further analysis showed that the observed associations with adverse perinatal outcome were also present and in the same direction for the risk of delivery before 32 weeks (Table 4). Fewer women with a cervical length of less than 38 mm delivered before 32 weeks (14%) compared to the control group (29%), while these percentages were comparable in women with cervical length of 38 mm or more: 10% versus 8%. This difference between women with short and long cervix in the effect of a pessary was statistically significant (P for interaction 0.04). As presented in Table 4, more women with monochorionic pregnancy delivered early without a pessary, and this risk was lower in the pessary group (OR 0.6). Parous women with at least one previous preterm birth (OR 3.8) and women having a triplet pregnancy (OR 1.8) were estimated to be at higher risk of delivery before 32 weeks when they had a pessary.

Developing the multivariable model

The multivariable model, including the four variables and their interaction with treatment, is presented in Table 5.

Performance of the model for risk prediction

The model's c-statistic, expressing its ability to discriminate between women with and without adverse perinatal outcome, was 0.71 (95% CI: 0.66-0.77). Internal validation, after correction for optimism by bootstrapping, showed acceptable discrimination, with a c-statistic of 0.69 (95% CI: 0.63-0.74). The calibration plot, comparing the optimism-corrected predicted probabilities with the observed frequencies of adverse perinatal outcome, indicated acceptable calibration (Online Supplement 2).

Performance of the model for identification of women who could benefit from pessary

Figure 3 depicts the distribution of the calculated differences in the risk of adverse perinatal outcome when using a pessary in the ProTWIN trial participants. Overall, 287 women had a positive risk difference and were considered to benefit from a pessary (35%; 95% CI: 32% to 39%). Calibration plot for the estimated and observed absolute risk differences showed an acceptable calibration as well (Online Supplement 2).

In women for whom the multivariable model predicts a benefit from a pessary, the average risk reduction was 15% (95% CI: 6% to 24%). For those predicted not to benefit from a pessary, the average perinatal risk reduction by avoiding a pessary was 8% (95% CI: 2% to 12%). We estimate that by application of a model-based pessary insertion, the risk of adverse perinatal outcome could reduce from 13.5% to 8.1% (5.4% risk reduction; 95% CI: 2.1% to 8.6%).

When we compared the model-based strategy with the cervical length-based strategy, 174 women would qualify for pessary insertion with both strategies (22%) while 505 women were not selected by both strategies (63%). In 129 participants (16%) the two strategies were discordant: 120 women would qualify for a pessary based on the multivariable model only (15%) while 9 other women would qualify for a pessary by cervical length only (1.1%). The estimated population risk of adverse perinatal outcome by the cervical length-based strategy is 11.2%. The model-based strategy led to a significantly lower risk of adverse perinatal outcome compared to the cervical length-based strategy (3.1% risk reduction (95% CI: 0.8% to 5.4%).

DISCUSSION

We have developed a multivariable treatment selection model that can be used for identifying women with multiple pregnancies who could benefit from a cervical

pessary. We found applying this model to be superior to a strategy based on cervical length only. The model we developed relies on cervical length, chorionicity, parity, history of preterm birth and number of fetuses to calculate the risk with and without a pessary. We estimated that the risk of adverse perinatal outcome, with decision-making about a pessary based on the calculated risk difference, would be 5.4% lower than a strategy of inserting a pessary for no one, and 3.1% lower compared to a strategy of inserting pessary in women with a short cervix only. The model presented in this study is simple; all the included variables are easy to measure and are known when the decision for pessary placement is to be made.

Our analysis is based on data collected in a randomized trial, consequently, there was no selection bias; none of the evaluated variables had affected the choice of treatment. We limited our analysis to four risk factors, which were specified for subgroup analysis in the trial protocol, thereby controlling the problem of multiple comparisons as well as the risk of spurious findings. Our approach differs from the conventional approach to do subgroup analysis in clinical trials, which has several well-recognized limitations[28, 29]. Most notably, subgroup analyses ignore the joint influence of variables.

A limitation, however, is that our proposed treatment selection model is based on an exploratory analysis using a single trial data. There is definitely a need for validating the model and its performance in other, independent trial datasets. To perform this validation a new trial should invite an unselected group of women with a multiple pregnancy and randomly allocate them to a pessary or a control group. This trial should include women with short cervix as well as long cervix, and women with and without history of preterm birth[30]. There is a reasonable chance that several such

trials will follow. At a meeting in February 2014 researchers from different countries presented their intended trial protocols regarding the use of pessary and showed their intention to cooperate together within the global obstetrics network (GONet)[31]. Such a cooperation would allow an external validation of model performance.

Another limitation is the number of missing cervical length measurements at baseline, which also differed between the pessary and control groups. The fact that more measurements were missing in the control group was probably because obstetricians were probably less aware that women in the control group were participating in the trial. As an additional visit was needed for placement of the pessary, there was an extra opportunity for cervical length measurement in the pessary group. Another factor associated with missing cervical length was a lower gestational age at recruitment. There were no further significant difference between women who had missing data on cervical length and those with cervical length measure. Both treatment and gestational age at recruitment along with all available baseline characteristics of women at study entry are included in the model to minimize the potential bias that could arise from data imputation. Furthermore, a sensitivity analysis showed that missing measurements did not alter the estimated effect of the cervical length, pessary and the interaction between pessary and cervical length.

Our analysis showed that apart from a short cervix other variables can also inform about the expected benefit from pessary insertion in an individual woman. Women who had monochorionic twins seemed to benefit from pessary insertion. They also had longer time to delivery when using a pessary, as especially deliveries earlier than 32 weeks were prevented by inserting a pessary. Other studies have shown that monochorionicity is a moderate risk factor for preterm birth in twins[32-34]. This may

explain why women at higher baseline risk could potentially benefit more from the intervention.

The other variable was a history of preterm birth, already known to be the strongest risk factor for preterm birth in future pregnancies. It is believed that some risk factors for preterm birth likely persist from pregnancy to pregnancy[14, 35, 36]. The association we observed in this study may seem counterintuitive. One can expect that because women with a history of a preterm birth are at higher risk of preterm delivery in their current pregnancy, they can be good targets for pessary insertion, since there is more room for a benefit. However, we observed a reverse association in this study: women with a history of preterm birth were actually at higher risk of preterm birth and an adverse perinatal outcome when they had received pessary. In a similar way, triplets are at a known higher risk of preterm delivery compared to twin pregnancies[37], and we observed similar association that in triplet pregnancies women who had received pessary had higher risk of adverse perinatal outcome.

The etiology of preterm delivery is multifactorial; the natural course of the disease and the turning point in which a treatment (like progesterone or pessary) can influence the causal pathway can vary[38, 39]. On the other hand, the exact mechanism by which cervical pessaries act is unknown. A cervical pessary surrounds the cervix and might therefore act by changing the inclination of the cervical canal, preventing premature dilatation of the cervix and rupture of the membranes or by protecting the cervical mucus plug and preventing ascending infections that lead to preterm delivery[40-42]. We can hypothesize that the causal pathway of preterm birth in women with a history of preterm birth differs from women with a monochorionic twin, triplet or a short cervical length at screening. This may explain why a pessary can be beneficial in some

groups of women, and not in other groups, where it potentially speeds up the causal pathway, for example by manipulation of the cervix during placement/or removal of the pessary. Studies on the effect of supplemental progesterone compounds also have shown such differences in the direction of the treatment effect, indicating that some pathways to preterm birth are not influenced by this therapy[43].

Our results give guidance for future research. At this moment trials on preterm birth prevention are mainly focused on high risk women, with the increase in risk being based on a short cervical length or a history of preterm birth. Although we do not yet fully understand the possible adverse effect of the pessary on woman with a history of preterm birth, found in our analysis, restriction of the inclusion criteria to this population may lead to an underestimation or contradictory result of the potential benefit of the pessary.

Despite the absence of a benefit from using a pessary in an unselected group of women with multiple pregnancies, our analysis suggests that about one out of three women would benefit from a pessary, and that a multivariable model can identify these women. Our model identified more benefiting women than using cervical length only for patient selection. Yet, before the model can be used for reliable guidance of medical decision making regarding pessary insertion, it needs to be successfully validated.

Contributors

SMSL, BWJM, and DJB designed and coordinated the main trial. MM, KWMB, JJD, BNB, MTMF, MAO, HCJS JMS, ES and MW collected data. PT, BWJM, PMB and MHZ conceived and designed this study. PT, MHZ and PMB analyzed and interpreted the data. PT and MHZ wrote the first draft of the manuscript. JH contributed in the

interpretation of the findings. All authors critically revised the first draft, and approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

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Figure legends

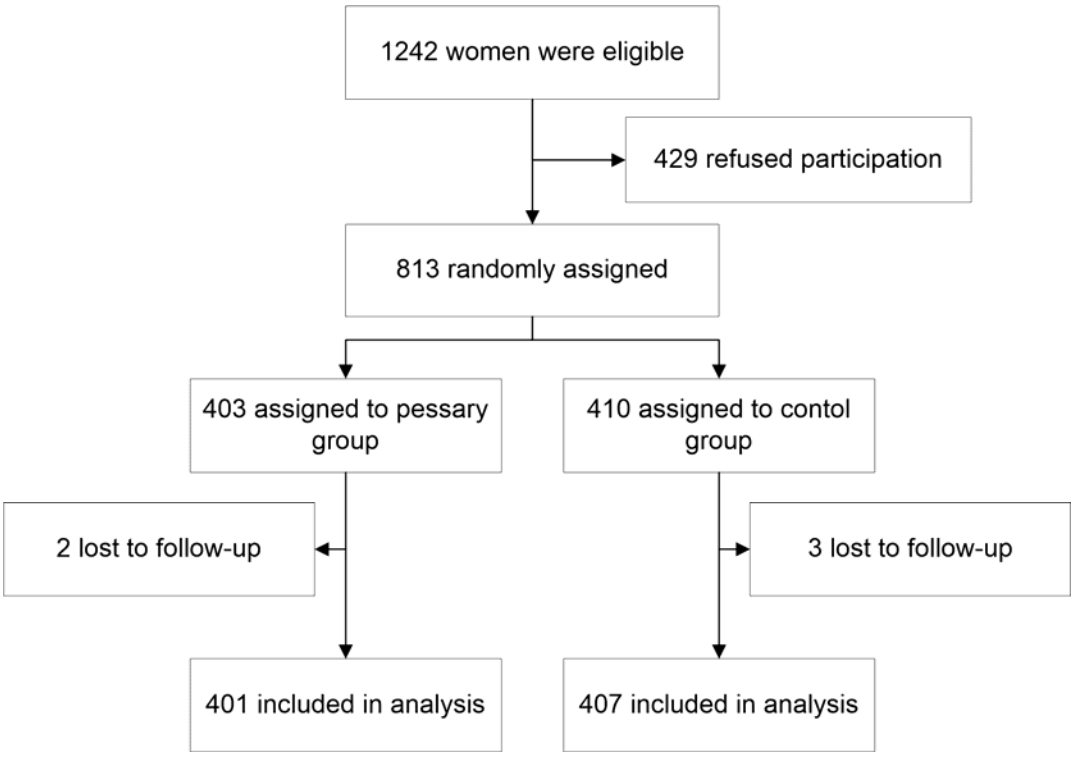


Figure 1. Trial profile.

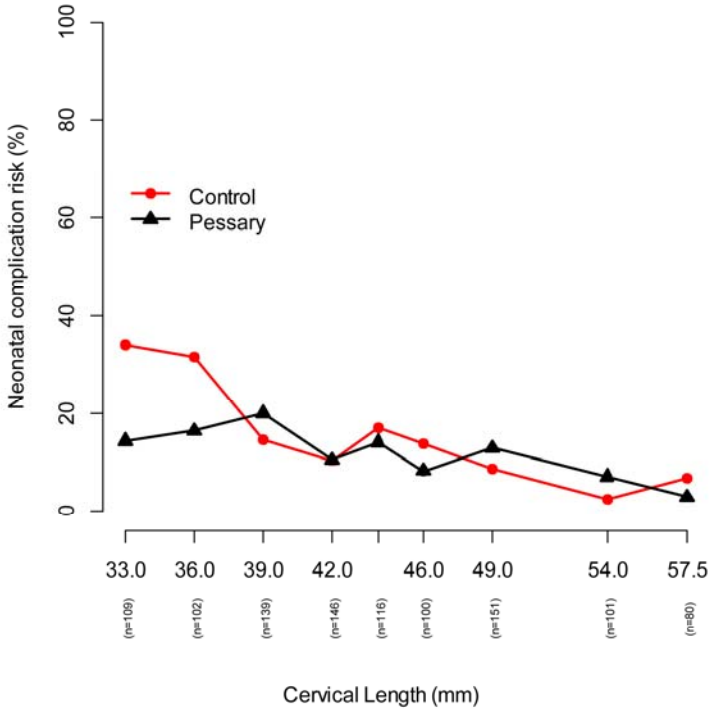


Figure 2. The empirical association between cervical length and the risk of adverse perinatal outcome, separately in women in whom pessary was inserted and the control group.

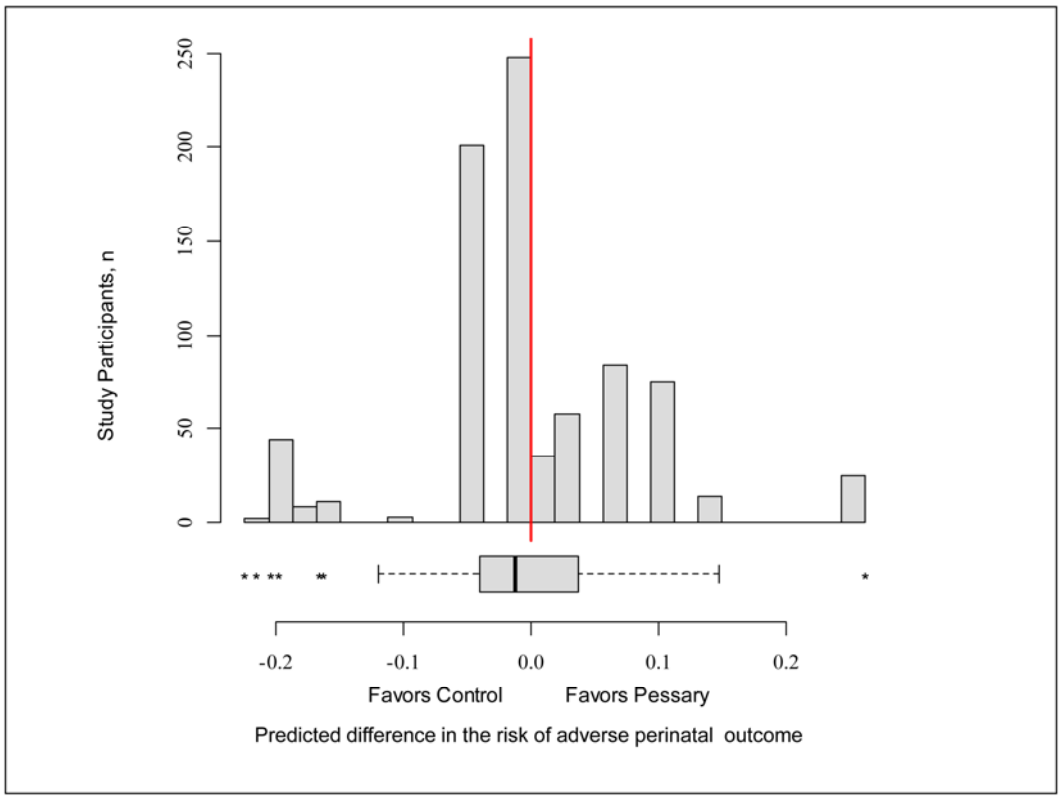


Figure 3. Distribution of the estimated risk reduction by pessary insertion.

Table 1. Baseline characteristics of the ProTWIN trial participants.

Baseline characteristics	Pessary group (n=401)	% missing	Control group (n=407)	% missing
Maternal characteristics				
Age at randomisation *(years)*	32.9 (30.1-36.3)	0	32.5 (30.0-35.9)	0
Body mass index at booking *(kg/m)*^{2}	23.7 (21.5-26.3)	9	22.9 (21.0-25.8)	8
Caucasian ethnicity	352 (87.3)	4	347 (84.6)	6
University or higher vocational education	153 (38.0)	40	156 (38.0)	40
Nulliparous	222 (55.1)	0	225 (54.9)	0.2
Previous preterm delivery	29 (7.2)	0.5	26 (6.3)	0.5
Smoking during pregnancy	16 (4.0)	2	25 (6.1)	3
Pregnancy characteristics				
Pregnancy after fertility treatment*	150 (37.2)	0.5	141 (34.4)	1
Triplets	9 (2.2)	0	9 (2.2)	0
Monochorionic pregnancy	87 (21.6)	0.2	100 (24.4)	1
Gestational age at randomisation *(weeks)*	17.0 (15.5-18.4)	0	17.2 (15.8-18.5)	0.5
Cervical length at randomization *(mm)*	43 (38-50)	19	44 (39-50)	29
Funnelling at randomisation	5 (1.2)	15	4 (1.0)	21

Data are median (interquartile range) or n(%). *Ovarian hyperstimulation, in-vitro fertilisation, intracytoplasmic sperm injection, or intrauterine insemination.

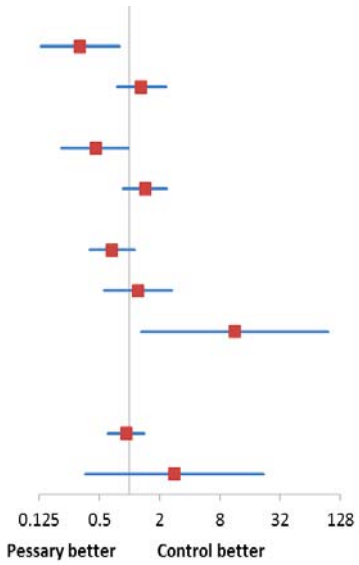
Table 2. Pregnancy, neonatal, and maternal outcomes in the participants of the ProTWIN trial

Outcomes	Pessary group (n=401)	Control group (n=407)	*RR (95% CI)*
Composite poor perinatal outcome	53 (13%)	55 (14%)	0.98 (0.69 to 1.39)
Stillbirth	10 (2%)	10 (2%)	1.02 (0.41 to 2.59)
Periventricular leucomalacia	0	5 (1%)	-
Respiratory distress syndrome	27 (7%)	18 (4%)	1.52 (0.85 to 2.72)
Bronchopulmonary dysplasia	2 (<1%)	6 (1%)	0.34 (0.07 to 1.67
Intraventricular haemorrhage	6 (1%)	5 (1%)	1.22 (0.37 to 3.98)
Necrotising enterocolitis	8 (2%)	6 (1%)	1.35 (0.47 to 3.88)
Sepsis	16 (4%)	18 (4%)	0.89 (0.45 to 1.77)
Death before discharge	16 (4%)	18 (4%)	0.90 (0.46 to 1.77)
Admission to neonatal intensive care unit	60 (15%)	76 (19%)	0.80 (0.57 to 1.13)
Gestational age at delivery (weeks)	36.7 (34·7 to 37·4)	36.4 (34.3 to 37.6)	0.91 (0.76 to 1.09) †
< 28 weeks	16 (4%)	21 (5%)	0.79 (0.50 to 1.27)
< 32 weeks	41 (10%)	49 (12%)	0.86 (0.65 to 1.15)
< 37 weeks	222 (55%)	233 (57%)	0.94 (0.87 to 1.07)
Birth weight			
<2500 g	271 (68%)	275 (68%)	0.99 (0.90 to 1.09)
<1500 g	49 (12%)	53 (13%)	0.93 (0.65 to 1.35)
Composite maternal morbidity	38 (9%)	32 (8%)	1.22 (0.77 to 1.92)

Data are presented as n (%) or median (IQR). NA=not applicable. †Hazard ratio instead of RR.

Table 3. Estimated risk of adverse perinatal outcome with and without pessary in subgroups defined by pre-specified risk factors

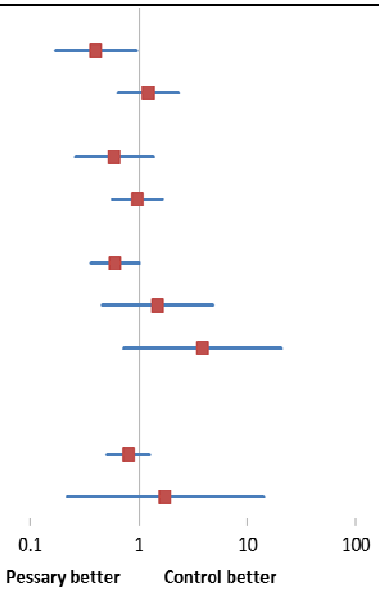
Potential Treatment Selection Factors	n	% Poor Perinatal Outcome		Odds Ratio (95% CI)	Odds Ratio (95% CI)	Interaction *P*-value
		Pessary	Control			
Cervical length						
< 38 mm	322	11.54	29.09		0.32 (0.13-0.79)	0.010
≥ 38mm	675	12.85	10.13		1.31 (0.75-2.30)	
Chorionicity						
Monochorionic	189	13.79	26.00		0.46 (0.21-0.97)	0.015
Dichorionic	621	13.06	9.51		1.43 (0.86-2.37)	
Obstetric history						
Nulliparous	445	13.12	18.30		0.67 (0.40-1.13)	
Parous with no previous preterm birth	308	9.93	8.28		1.22 (0.56-2.66)	0.009
Parous with at least one previous preterm birth	55	31.03	3.85		11.25 (1.31-96.4)	
Number of foetuses						
Twin	790	12.50	13.32		0.98 (0.61-1.41)	0.301
Triplet	18	44.44	22.22		2.8 (0.36-21.73)	



CI, confidence interval
Values presented in the table are based on observed data before multiple imputation.

Table 4. Estimated risk of delivery before 32 weeks with and without pessary in subgroups defined by pre-specified risk factors

Other Potential Treatment Selection Factors	n	% delivery <32 weeks		Odds Ratio (95% CI)	Odds Ratio (95% CI)	Interaction *P*-value
		Pessary	Control			
Cervical length						
< 38 mm	322	14.10	29.09		0.40 (0.17-0.95)	0.040
≥ 38mm	675	9.64	8.02		1.22 (0.65-2.30)	
Chorionicity						
Monochorionic	189	11.49	18.00		0.59 (0.26-1.36)	0.327
Dichorionic	621	9.87	10.16		0.97 (0.57-1.64)	
Obstetric history						
Nulliparous	445	12.22	18.75		0.60 (0.36-1.02)	
Parous with no previous preterm birth	308	4.64	3.18		1.48 (0.46-4.76)	0.002
Parous with at least one previous preterm birth	55	24.14	7.69		3.82 (0.72-20.4)	
Number of foetuses						
Twin	790	9.69	11.81		0.80 (0.51-1.26)	0.475
Triplet	18	33.33	22.22		1.75 (0.22-14.22)	



CI, confidence interval
Values presented in the table are based on observed data before multiple imputation.

Table 5. Multivariable model for the prediction of adverse perinatal outcome.

Predictor	**OR (95% CI) ****	**Beta***
Intercept		-2.21
Main terms		
Pessary	1.25 (0.62-2.52)	0.22
Cervical length <38 mm	2.92 (1.36-6.26)	1.07
Monochorionic	3.35 (1.79-6.28)	1.21
Parous with no previous preterm birth	0.44 (0.22-0.87)	-0.83
Parous with at least one previous preterm birth	0.23 (0.03- 1.82)	-1.46
Triplet	1.77 (0.33- 9.36)	0.57
Interaction terms		
Pessary × Cervical length <38 mm	0.36 (0.13-1.03)	-1.01
Pessary × Monochorionic	0.30 (0.12-0.76)	-1.22
Pessary × Parous with no previous preterm birth	1.72 (0.66-4.48)	0.54
Pessary × Parous with at least one previous preterm birth	14.01 (1.50-130.9)	2.64
Pessary × Triplet	3.67 (0.42-32.32)	1.30

*Shrunken with an average shrinkage factor of 0.76

** Because of the small size of some subpopulations, the ORs indicate general directions but might not work accurately in extreme scenarios involving these subpopulations (e.g triplets).