EUROX 24 (2024) 100343

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology: X

journal homepage: www.journals.elsevier.com/european-journal-of-obstetrics-and-gynecology-and-reproductive-biology

Effects of nationwide adjustment of tocolysis protocol in the Netherlands on neonatal outcomes in women with threatened preterm birth and delivery at 30-32 weeks of gestation: A cohort study

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ARTICLE INFO

Keywords:
Threatened preterm birth
Tocolysis
Neonatal outcome
Tocolytics

ABSTRACT

Objective: In 2019 the Dutch national prevention of preterm birth (PTB) protocol was adjusted to withhold tocolysis for threatened PTB above 30 weeks of gestation due to insufficient evidence regarding its effectiveness on improving perinatal outcomes. The aim of this study is to evaluate neonatal outcomes of children born in the Netherlands between 30 and 32 weeks of gestation before and after the national protocol change.

Study design: We performed a nationwide retrospective cohort study comparing outcomes of births in the years 2018 (tocolysis) and 2020 (no tocolysis). Tocolytic therapy consisted of either nifedipine or atosiban. Data were extracted from the national Perinatal Registry (PERINED). Women with a spontaneous PTB from 30 + 0 to 31 + 6 weeks of gestation were included. The primary outcome was a composite of mortality, severe intraventricular hemorrhage, severe necrotizing enterocolitis, cystic periventricular leukomalacia, and retinopathy of prematurity needing therapy. Secondary outcomes included additional neonatal outcomes. The odds ratio (OR) with corresponding 95 % confidence interval (CI) was calculated by logistic regression analysis for the year 2020 compared with 2018.

Results: Composite neonatal outcome did not differ between 2018 compared to 2020 (8.4 % (18/215) vs 8.2 % (25/306), OR 0.95; 95 % CI 0.51–1.77). No difference in composite neonatal outcome was found when analyzing groups as singletons (7.1 % vs 9.3 %, OR 1.35; 95 % CI 0.64–2.87), and multiples (13.3 % vs 5.9 %, OR 0.41; 95 % CI 0.13–1.26).

Conclusion: There was no significant difference in composite neonatal outcome in pregnancies resulting in spontaneous PTB between 30 and 32 weeks of gestation in 2018 (with tocolysis) compared to 2020 (no tocolysis). These results support the protocol adjustment to withhold tocolytic treatment in women with threatened PTB above 30 weeks of gestation.

Introduction

Preterm birth (PTB) is the most common cause of neonatal mortality and morbidity. Although many children survive, short- and long-term complications remain throughout adult life. Establishing optimal preventive treatments of (threatened) PTB and its subsequent complications is therefore crucial in preventing neonatal mortality and morbidity [1, 2].

A commonly used treatment to prolong pregnancy in case of threatened PTB is the use of tocolytic therapy. The two main tocolytic drugs used in clinical practice are oxytocin receptor antagonists (atosiban) and calcium channel blockers (nifedipine). Treatment goals of

Abbreviations: CI, Confidence interval; CPAP, Continuous positive airway pressure; GA, Gestational age; GBS, Group B streptococcus; IVH, Intraventricular hemorrhage; NEC, Necrotizing enterocolitis; NICU, Neonatal Intensive Care Unit; OR, Odds ratio; PERINED, The Netherlands Perinatal Registry; PPROM, Premature preterm rupture of the membranes; PTB, Preterm birth; PVL, Periventricular leukomalacia; RDS, Respiratory distress syndrome.

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https://doi.org/10.1016/j.eurox.2024.100343
Received 15 February 2024; Received in revised form 11 September 2024; Accepted 23 September 2024
Available online 24 September 2024
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tocolysis include transportation to a facility with a Neonatal Intensive Care Unit (NICU) and determination of group B streptococcus (GBS) status, but most importantly to administer a (complete) course of corticosteroids for fetal lung maturation [3]. Corticosteroids have been proven to be effective in improving neonatal outcomes in case of PTB by reducing the risk of mortality and severe morbidity [4–11]. Corticosteroids require a therapeutic period of 48 h to be most effective, but even an incomplete course can improve neonatal outcomes [11]. While tocolysis may prolong the pregnancy for 48 h, an association between tocolysis and improved neonatal outcomes has not been demonstrated in previous studies. Before 2019 tocolytics as treatment for threatened PTB till 34 weeks' gestation was part of standard care in Dutch guidelines. However, regional guidelines were revised in 2019 as it was concluded that although various randomized clinical trials concerning tocolytics exist, none of these studies were able to demonstrate a positive effect on neonatal outcomes [12–14]. In addition, internationally there is great variety regarding tocolytics, as in various regions tocolytics are not used. Thus, in 2019, the national Dutch protocol was adjusted to exclude tocolysis as treatment for threatened PTB after 30 weeks of gestation.

The aim of the current study is to evaluate neonatal outcomes of children born in the Netherlands between 30 and 32 weeks of gestation in the year before and after the protocol adjustment in 2019. These results will contribute to determine the effectiveness of tocolytic therapy for threatened PTB.

Methods

Study design

This was a nationwide retrospective cohort study in the Netherlands evaluating neonatal outcomes before and after the protocol adjustment wherein standardized administration of tocolytics for threatened PTB above 30 weeks of gestation was discontinued. Temporary tocolytics could still be administered during transfer to a specialized center with NICU facilities. Guidelines regarding corticosteroids administration were unchanged, meaning that every woman with a threatened PTB before 34 weeks gestation still received corticosteroids. Throughout 2019, the exact moment of the new protocol implementation differed between the nine regions of the Netherlands. Data from 2019 were therefore excluded. Pregnancy outcomes of the year 2018 were compared to outcomes of the year 2020. During 2018 tocolysis was administered per protocol for 48 h with either nifedipine or atosiban. During 2020 tocolysis was administered in case of threatened PTB before 30 weeks' gestation. The manuscript is reported following Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [15].

Study population

Children born from a spontaneous PTB of singleton or multiple pregnancy from 30^{+0} up to 31^{+6} weeks of gestation were included. According to Dutch protocol, women with threatened PTB before 32 weeks of gestational age (GA) should be transferred to a specialized perinatal center with a NICU. Since pediatricians in NICU centers register all admissions and perinatal outcomes, GA at birth was limited to 30^{+0} up to 31^{+6} weeks of gestation in the current study. Exclusion criteria were 1) iatrogenic-induced delivery or an unknown start of labor, 2) antepartum fetal deaths, 3) infants with structural, congenital, or chromosomal abnormalities, 4) maternal age $<$ 18 years, and 5) as one healthcare region continued with tocolytic treatment after 2019, pregnancies from this region were excluded from main analysis.

Data collection

Data were extracted from the Netherlands Perinatal Registry (PERINED) [16], This database contains population-based data on obstetric history, pregnancy, and neonatal and maternal outcomes of 98 % of all pregnancies in the Netherlands. Permission for this specific research question was given in spring 2022 by PERINED with approval name "Project 22.07″. Data analysis started on the 22nd of July 2022 and was finalized on the 30th of December 2023.

Outcome measurements

The primary outcome was a composite neonatal outcome consisting of intrapartum and neonatal mortality within 28 days of life, intraventricular hemorrhage (IVH) >2B, necrotizing enterocolitis (NEC) ≥ stage 2, cystic periventricular leukomalacia (PVL) > grade 1, and retinopathy of prematurity > grade 2 or needing laser therapy [17–20]. The primary outcome was assessed on child level and measured as composite (i.e. if an infant has more than one of the components of the primary outcome, this will be accounted for as one primary outcome).

Secondary neonatal outcomes include separate components of our primary outcome, Apgar score <7, NICU admission for more than 24 h, unproven early-onset sepsis, blood culture-proven late-onset sepsis, hearing loss, respiratory distress syndrome (RDS) needing surfactant therapy, use of invasive mechanical ventilation and continuous positive airway pressure (CPAP), convulsions, and pneumothorax [21]. The core outcome set for studies evaluating interventions to prevent PTB was used as a guideline to define outcomes in this study [22]. The baseline characteristic socio-economic status (SES) was based on data from the Netherlands Institute of Social Research, which was linked to women's four-digit zip code and divided in quintiles. Low SES is the first quintile.

Statistical analysis

The primary outcome was assessed on infant level using a log-binomial generalized estimating equations (GEE) model to account for correlation of multiples [23]. Mothers were considered as cluster variables to account for interdependence between outcomes. Components of the primary outcome were similarly analyzed. We reported odds ratio (OR) with corresponding 95 % confidence interval (CI) of the outcome measure with the year 2018 as the reference. Rate of each outcome measure was calculated expressed as number with corresponding percentage for both groups. Categorical outcomes were compared using the chi-square test. Continuous outcomes were expressed by mean with standard deviation and, if normal distributed, a t-test was used to determine statistical significance. The secondary outcomes were analyzed by logistic regression analysis. Only the combined outcome measurements analysis was adjusted for maternal age. Significance for all analysis was set at a p-value < 0.05.

In subgroup analyses, births from singleton and multiple pregnancies were analyzed separately. Furthermore, a sensitivity analysis was performed wherein 2020 pregnancy outcomes of the excluded healthcare-region that continued standardized tocolytic therapy were compared with the 2020 group (no tocolysis).

Results

In total 329,357 children were born in the years 2018 and 2020. After applying our inclusion and exclusion criteria, a total of 444 births were included of which 191 births were in 2018, resulting in 215 children, and 253 births in 2020, resulting in 306 children. The flowchart can be found in Fig. 1.

Characteristics

Baseline maternal and obstetric characteristics were mostly similar for both years, also when looking at singletons and multiples separately (Table 1 and Appendix Table S1). However, a significant difference was observed in amount of singleton births in 2018 compared to 2020 (89.0 % (170/191) vs 80.6 % (204/253), p = 0.02).

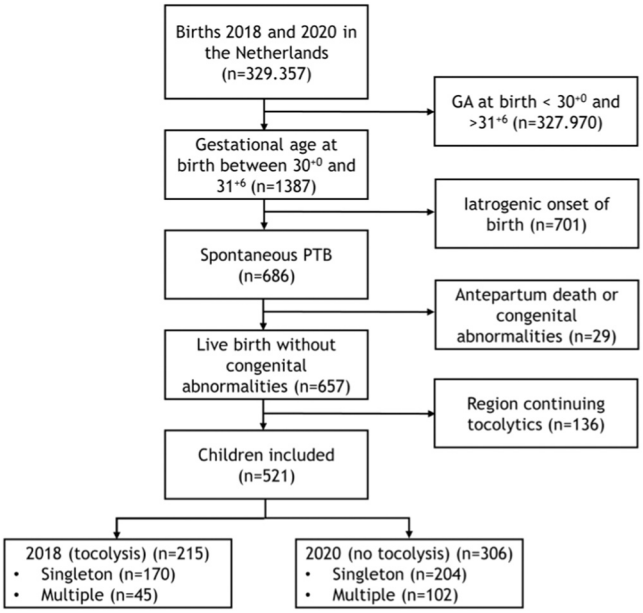

Fig. 1. Flowchart of inclusions. GA: gestational age. sPTB: spontaneous preterm birth.

Table 1
Baseline characteristics.

	2018 with tocolysis		2020 without tocolysis		
	Children n = 215		Children n = 306		
Maternal	n/N (%) or mean (SD)		n/N (%) or mean (SD)		*p-value*
Women	N = 191		N = 253		
Maternal age, years	30.9	(4.7)	30.3	(5.1)	0.22
Ethnicity					0.54
Western	136/191	(71.2)	190/253	(75.1)	
Mediterranean	5/191	(2.6)	8/253	(3.2)	
Other non-western	50/191	(26.2)	55/253	(21.7)	
Low socio- economic status*	39/191	(20.4)	62/253	(24.5)	0.31
Parity					0.31
Nulliparous	104/191	(54.5)	150/253	(59.3)	
Multiparous	87/191	(45.5)	103/253	(40.7)	
Obstetric					
Composition of pregnancy					0.02
Singleton	170/191	(89.0)	204/253	(80.6)	
Multiple	21/191	(11.0)	49/253	(19.4)	
PPROM	59/191	(30.9)	94/253	(37.2)	0.17
Fever during labor	3/191	(1.6)	11/253	(4.3)	0.10

Rate shown as number per total number of women included.
†Shown as mean with standard deviation
SD: standard deviation. PPROM: premature preterm rupture of the membranes.
*Socio-economic status was calculated in 5 quintiles based on data from the Netherlands Institute of Social Research, linked to women's home addresses, with "Low" being the first quintile.

Primary outcome

We found no significant difference in the composite neonatal outcome, with a rate of 8.4 % (18/215) in 2018 and 8.2 % (25/306) in 2020 (OR 0.95; 95 % CI 0.51–1.77). Neonatal mortality was 3.7 % (8/215) in 2018 compared with 1.3 % (4/306) in 2020 (OR 0.34; 95 % CI 0.10–1.13). Also, when looking at the separate components of the composite outcome, no significant difference in any of the morbidities was found (Table 2).

Secondary outcome

Almost all children were born in a specialized center with NICU facilities. Most children were admitted to the NICU for longer than 24 h during both years (83.3 % in 2018 vs 84.6 % in 2020, p = 0.67). A significant increase in the use of CPAP was observed, from 76.7 % (165/215) of children in 2018 compared with 84.0 % (257/306) of children in 2020 (p = 0.04). The incidence of late onset sepsis was higher in the year 2020 compared with 2018, although not significant (5.9 % vs 2.3 %, p = 0.05). Also, in other secondary outcomes no significant difference could be observed, including surfactant treatment for RDS and use of invasive mechanical ventilation (Table 3).

Subgroup analyses

Analyzing singletons separately, we found no significant difference in composite neonatal outcome between the groups, with a rate of 7.1 % (12/170) in singletons born in 2018 and 9.3 % (19/204) in singletons born in 2020 (OR 1.35; 95 % CI 0.64–2.87). Investigating the components separately, a higher rate of cystic PVL was found in the 2020 no-tocolytic group of 2.9 % (6/204) compared with zero children (0/170) in 2018 (p = 0.02) (Appendix Table S2). Also in multiple births, we found no significant difference in composite neonatal outcome with 13.3 % (6/45) in 2018 and 5.9 % (6/102) in 2020 (OR 0.41; 95 % CI 0.13–1.26) (Appendix Table S3).

Sensitivity analysis

As stated previously, protocol regarding tocolytic administration was unchanged in one health-care region. When comparing neonatal outcomes of 2020 in this region with our 2020 group (no tocolysis), no significant difference in composite neonatal outcome was observed (Appendix Table S4).

Table 2
Primary outcome.

	2018 with tocolysis		2020 without tocolysis			
	n = 215		n = 306			
	n	(%)	n	(%)	*p-value*	OR (CI 95 %)
Composite neonatal outcome	18	(8.4)	25	(8.2)	0.88	0.95 (0.51 – 1.77)
Neonatal mortality <28 days	8	(3.7)	4	(1.3)	0.08	0.34 (0.10 – 1.13)
Neonatal mortality <7 days	6	(2.8)	2	(0.7)	0.07	0.23 (0.05 – 1.12)
IVH > grade 2B	4	(1.9)	4	(1.3)	0.62	0.70 (0.17 – 2.84)
PVL > grade 1	2	(0.9)	8	(2.6)	0.19	2.85 (0.60 – 13.50)
NEC ≥ stage 2	6	(2.8)	12	(3.9)	0.51	1.40 (0.52 – 3.73)
ROP needing therapy	1	(0.5)	0	(0.0)	NA	NA

OR: odds ratio. CI: confidence interval. IVH: intraventricular hemorrhage. PVL: periventricular leukomalacia. NEC: necrotizing enterocolitis. ROP: retinopathy of prematurity. NA: not applicable.

Table 3
Secondary outcomes.

	2018 n = 215		2020 (n = 306)		
Obstetric outcomes	n (%) or mean (SD)		n (%) or mean (SD)		*p-value*
Type of delivery					0.39
Vaginal	153	(71.2)	207	(67.6)	
Cesarean	62	(28.8)	99	(32.4)	
Location of birth					0.23
Specialized center*	210	(97.7)	290	(94.8)	
General hospital	4	(1.9)	11	(3.6)	
Unknown	1	(0.5)	5	(1.6)	
Neonatal outcomes					
Fetal sex, male	119	(55.3)	170	(55.6)	0.96
GA at birth	31^{+0}	(3.9)	31^{+0}	(4.1)	0.48
Birth weight, grams	1654.0	(232.2)	1659.5	(235.6)	0.79
Weight adjusted for GA[†]					
P > 90	12	(5.6)	17	(5.6)	0.99
P < 10	24	(11.2)	30	(9.8)	0.61
Apgar score (mean)[‡]	8.1	(1.7)	8.3	(1.5)	0.47
Apgar score < 7[‡]	34	(15.8)	32	(10.5)	0.07
NICU admission > 24 h	179	(83.3)	259	(84.6)	0.67
Early onset sepsis	6	(2.8)	10	(3.3)	0.76
Late onset sepsis[#]	5	(2.3)	18	(5.9)	0.052
Hearing loss[§]	24	(11.2)	26	(8.5)	0.31
Surfactant therapy	32	(14.9)	55	(18.0)	0.35
Invasive ventilation	12	(5.6)	15	(4.9)	0.73
Duration, days	3.3	(1.9)	1.7	(2.5)	0.27
CPAP	165	(76.7)	257	(84.0)	0.04
Convulsions	1	(0.5)	0		0.23
Pneumothorax	2	(0.9)	3	(1.0)	0.95

SD: standard deviation. GA: gestational age. CPAP: continuous positive airway pressure. NICU: Neonatal Intensive Care Unit.
*With NICU facilities
[†]Birth weight distributed by percentile, adjusted for gestational age.
[‡]After five minutes
[#]Blood culture proven
[§]Hearing loss at automated brainstem response screening

Discussion

Findings

In this retrospective cohort study including 521 children from 444 pregnancies, we found no significant difference in composite neonatal outcome in pregnancies resulting in spontaneous PTB between 30 and 32 weeks of gestation in 2018 (with tocolysis) compared with 2020 (no tocolysis). This result is persistent when investigating singleton and multiple pregnancies separately and in regional sensitivity analysis. Likewise, when investigating the separate components of the composite outcome no significant difference in mortality or any of the morbidities was observed, except for a significant higher rate of cystic PVL in the singleton subgroup in 2020 compared with 2018.

Strengths and limitations

The study has several strengths. Our results are based on a national registry with a completeness of 98 % wherein registration of neonatal outcomes by NICU pediatricians is compulsory**.** The patient group in our study is well-defined, and bigger than most studies in the tocolysis research line, therefore better at detecting relevant outcomes. Our composite neonatal outcome considers the competing risk between mortality and multiple severe neonatal morbidities. It includes well-defined diagnoses and follows established core outcome sets [22,24]. Furthermore, we controlled for a possible regional difference in 2020, when one of the bigger regions continued with tocolytic therapy, providing additional sensitivity analysis.

Several limitations exist. First, we investigated pregnancies resulting in births between 30 and 32 weeks of gestation. However, a proportion of pregnancies with threatened preterm labor does not result in a birth before 32 weeks. Studies report that in case of threatened PTB between 28 to 33 weeks' gestation, only half delivers within 48 h and 61 % within seven days. The remaining portion will not deliver in the acute setting [25]. We could hypothesize that these women experience most benefit of tocolytic treatment due to prolongation of pregnancy, but if GA exceeded 32 weeks, outcomes were not included in our study. Also, concerning our 2020 no-tocolysis group, some women might have experienced threatened PTB before 30 weeks of gestation and therefore could have received tocolysis since standardized tocolytic treatment before 30 weeks of gestation was unchanged in the Dutch prevention of PTB protocol. Furthermore, during 2020 the placebo controlled randomized APOSTEL 8 trial was ongoing in which women with threatened PTB after 30 weeks' gestation could have received tocolysis if randomized in the atosiban group [26]. Unfortunately, administration of tocolysis is not registered in the national PERINED data registry utilized for the current study. As a result, we do not have any data on the effects of tocolytics on prolongation of pregnancy. Specific details on type of tocolytic therapy (nifedipine or atosiban) are also unknown, though studies indicate that neonatal outcomes do not differ between both therapies [27,28]. Although our cohort is bigger than most studies investigating neonatal outcomes after tocolysis, number of neonatal outcomes are still low and might have been too small to detect significant differences. Also, as the worldwide COVID-19 pandemic started in the end of 2019, societal changes and unique public health measures implemented during this period might have influenced results of the 2020 no-tocolytic group. However, our sensitivity analysis showed no difference between regions in 2020 and currently no studies report differences in neonatal outcomes after pregnancies infected by COVID-19 [29]. Additionally, we were limited to short-term neonatal outcomes. Well-defined long-term outcomes are not registered in the PERINED database and were therefore not obtainable in our research.

Interpretation

The rates of mortality and morbidities observed in our cohort are comparable to rates in other high-income countries [30,31]. However, results are not easily compared with current literature regarding neonatal outcomes after tocolysis, as research is heterogeneous and limited. Most studies include pregnancies with a wide range of GA. More importantly, the most common outcome is prolongation of pregnancy, as the main reason for tocolytic therapy in threatened PTB is delaying birth to administer corticosteroids for lung maturation and transportation of pregnant women to a specialized center [3]. However, when neonatal outcomes do not improve, the relevancy of prolongation should be questioned. We did not observe a difference in composite adverse neonatal outcome when comparing our 2018 tocolytic and 2020 no tocolytics group. Examining our outcomes more closely, we found no indication for improved lung maturation, as use of surfactant treatment for RDS and number of births in specialized centers with a NICU facility was similar in both groups. When looking at two previous placebo-controlled trials investigating the effects of nifedipine for threatened PTB between 24 and 34 weeks of gestation, they also did not observe improved neonatal outcomes in the nifedipine group. Both studies included women with lower GA compared to our study, where most benefit of administration of tocolytics and thus complete course of corticosteroids is to be expected [32,33]. Another placebo-controlled trial that investigated the effects of nifedipine in threatened PTB based on premature preterm rupture of the membranes (PPROM), found a lower rate of bronchopulmonary dysplasia in the tocolysis group ($p = 0.03$). However, the study was underpowered for this outcome and the tocolysis group had a higher GA at study entry [34]. Additionally, one placebo-controlled randomized controlled trial investigating the effects of atosiban in threatened PTB between 20 and 37 weeks of gestation found no significant difference in RDS [35]. In contrast, a retrospective cohort analysis using propensity score matching compared the effects of atosiban or nifedipine to placebo. The study found a

significantly higher rate of the composite mortality and severe IVH in children without tocolytic exposure compared to those with tocolytic exposure. This was a secondary outcome and baseline characteristics including corticosteroids, magnesium sulfate, and birth in a specialized center were all in favor of the tocolysis group. They accounted for this through propensity score matching to control for indication bias, but differences in some of the confounding factors persisted, requiring caution when interpreting these results [28].

In our study, we observed a significant increase in the use of CPAP in the 2020 no tocolysis group compared to the 2018 tocolysis group. This has not been reported in previous studies. Clinical relevance of this outcome can be questioned, since need for surfactant therapy and invasive ventilation can be considered as more reliable indicators for fetal lung maturation. These outcomes were similar in both groups. In the 2020 no tocolysis group, rate of late-onset sepsis was higher compared to the 2018 tocolysis group, almost reaching significance. Two possible explanations are the increased rates of PPROM and fever during labor which were observed in 2020, both of which are risk factors for neonatal sepsis, although neither was significantly elevated [36,37]. Recent trends in incidence of neonatal sepsis in preterm infants in the Netherlands are currently not available, though global trends show a rising incidence of neonatal sepsis, which might influence our results [38]. We found a significantly higher rate of PVL in singletons in the 2020 no tocolysis group compared to the 2018 tocolysis group. This has not been observed in previous literature. One possible explanation for the increased rate of PVL is the higher rate of maternal fever during labor in this group, which is a clinical sign of chorioamnionitis. Chorioamnionitis is associated with an increased risk on development of PVL. Secondly, tocolysis might have prolonged pregnancy, increasing effects of treatment with antenatal corticosteroids. However, data on antenatal corticosteroid and duration between tocolysis and birth was not available in the current study [39].

Unfortunately, results of the multiples cannot be compared with current literature since neonatal outcomes have not been published separately. In our cohort, the direction of the effects seems different for multiple births compared to singletons, with an increase in composite neonatal outcome in 2020 among children from singleton births and a decrease among children from multiple births. Therefore, we advocate for separate analysis of singleton and multiple pregnancies, as preventive therapy might differ.

Conclusions

In conclusion, when comparing neonatal outcomes of births between 30 and 32 weeks of gestation in the year 2018, when tocolytic therapy was part of protocol, to births in 2020, when standardized tocolytic therapy was omitted for threatened PTB after 30 weeks' gestation, no significant difference was found in composite neonatal outcome. More research is needed to determine effectiveness of tocolytic therapy on improved neonatal outcome in women with a threatened PTB.

CRediT authorship contribution statement

L. I. Van der Windt: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **J. A.L. Meliezer:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **W. Onland:** Writing – original draft, Investigation, Formal analysis, Conceptualization. **A. C.J. Ravelli:** Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **M. A. Oudijk:** Writing – original draft, Investigation, Formal analysis, Conceptualization.

Funding information

No funding sources.

Declaration of Competing Interest

None of the authors report any potential conflicts of interest for the present manuscript.

Acknowledgments

Not applicable.

Author contributions

JM, LvdW and AR participated in protocol development, data collection, data analysis, data interpretation, and writing. WO and MA participated in protocol development, data analysis, data interpretation, and writing. All collaborators saw and approved the final version. All collaborators were sent the paper as prepared for submission and given the opportunity to comment on the draft manuscript.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.eurox.2024.100343.

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