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ORIGINAL RESEARCH ARTICLE

Perinatal outcomes after therapeutic rest in the latent phase of labor: A cohort study

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Abstract

Introduction: Therapeutic rest refers to the usage of medication to relieve pain in women in the latent phase of labor. Very few data are available to evaluate the safety and effect of its use.

The objectives of this study were to compare perinatal and labor outcomes in women who were seeking hospital care during the latent phase of labor and who were treated either with or without therapeutic rest.

Material and methods: Retrospective cohort study with inclusion of nulliparous singleton pregnant women in the latent phase of labor presenting at the labor ward at Aarhus University Hospital, Denmark from May 13, 2018 to June 1, 2021. We identified two groups: women who were treated with therapeutic rest and women who were not. The primary outcomes were neonatal admission and neonatal resuscitation. Secondary outcomes included use of cardiotocography during labor, nonreactive fetal heart rate, meconium-stained amniotic fluid, pediatric delivery room assistance, umbilical cord arterial pH and standard base excess, Apgar score at 5 minutes, interventions during labor and mode of delivery.

Results: In our sample of 800 women in the latent phase of labor, 414 women (52%) were treated with therapeutic rest and 386 women (48%) were not. The most frequently used ($n = 206$) medication for therapeutic rest was a combination of paracetamol, triazolam and codeine. We found no significant difference in neonatal admission (9.2% vs 6.5%, adjusted odds ratio [aOR] 1.2, 95% confidence interval [CI] 0.4–3.1) or neonatal resuscitation (2.4% vs 3.1%, aOR 0.7, 95% CI 0.1–4.0) between women treated with or without therapeutic rest. There were no differences between the two groups in other perinatal adverse outcomes, interventions during labor or mode of delivery.

Conclusions: This study found no significant association between therapeutic rest and neonatal admission or resuscitation. Our findings indicate that therapeutic rest is

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; CTG, cardiotocography; IQR, interquartile range; NICU, neonatal intensive care unit; OR, odds ratio.

a safe method for managing the latent phase of labor concerning neonatal health and does not increase the risk of labor complications.

KEYWORDS
labor analgesia, latent labor, perinatal adverse outcomes, perinatal morbidity, therapeutic rest

1 | INTRODUCTION

The latent phase of labor is a process characterized by painful uterine contractions accompanied by effacement of the cervix and dilatation of the orifice.[1,2] Pain, exhaustion and the need for rest or sleep are described as important challenges in women's experience of the latent phase, and many women seek care at labor wards during the latent phase of labor.[3,4] In Denmark, these women are often treated as outpatients and return home, thus reducing the delivery room load and the number of obstetric interventions associated with early admission.[4–7] Most often, advice about non-pharmacological interventions such as showers, relaxation and massage is given, and if these measures are not considered sufficient, midwives can decide to offer the woman therapeutic rest.[8]

In this study we define therapeutic rest such as use of morphine, other opioid or opioid analogs, and/or sedative medication, alone or in combination with simple analgesics to relieve pain, exhaustion or anxiety, and to attain rest or sleep and used in the latent phase.[9–11] In Denmark, along with other Nordic countries, up to 21% of all pregnant women are treated with therapeutic rest during labor consisting of mild analgesics, opioid analgesics and hypnotics/sedatives in various predefined combinations.[8,12] This is in contrast to the recommendation from the Danish Society of Obstetrics and Gynecology to use an individual pharmacological treatment, preferably drugs with short half-lives and in the lowest possible dose.[13] In the USA, therapeutic rest is offered less frequently (1%) and often includes opioids or sedatives with or without antiemetics.[10,13]

There are a number of medications used individually or more often in combination for therapeutic rest in Denmark consisting of paracetamol, opioids (morphine or codeine), benzodiazepines (triazolam, zolpidem, etc.) and/or tocolytics (terbutaline, nifedipine); however, the composition of the medication for therapeutic rest varies between hospitals.[8,13] We found no international guidelines on the use of therapeutic rest.

Potential adverse effects of opioids and hypnotics/sedatives administered close to delivery may include absent fetal breathing movements,[15] respiratory depression in the neonate by opioids[16,17] and neonatal hypothermia and hypotonia caused by sedatives.[18–20] Only a few smaller studies assessing neonatal, maternal and labor effects of therapeutic rest have been published.[10,14,21] None of these studies found an association between the use of therapeutic rest and adverse perinatal outcomes. Thus, despite its common use, data and knowledge regarding both the safety and the effect of combined medication for therapeutic rest remain limited.[8]

Key message

There was no difference in perinatal adverse outcomes among women who were treated with therapeutic rest compared to women who were not. Therapeutic rest is a safe method for managing the latent phase of labor concerning neonatal health.

The objectives of this study were to compare perinatal and labor outcomes in women who were seeking hospital care during the latent phase of labor and who were treated either with or without therapeutic rest.

2 | MATERIAL AND METHODS

2.1 | Study design

This study was a retrospective cohort study conducted at the Department of Obstetrics and Gynecology, Aarhus University Hospital.

Maternity care in Denmark is free of charge, includes routine antenatal consultations, and women are provided with a direct phone number to their affiliated labor ward. If women are offered therapeutic rest during the latent phase of labor, the medication is handed out at the labor ward free of charge and they either take the medication at the labor ward or when they return home.

We scrutinized hospital admission records back in time to identify all nulliparous singleton pregnant women seeking care at the labor ward during the latent phase of labor, and continued until we reached the targeted sample size for our study. We defined the latent phase as painful contractions and a cervical dilatation <4–6 cm. The women in this study were seen at the labor ward between May 13, 2018 and June 1, 2021. We excluded parous women, women in active labor, with multiple pregnancies, women with scheduled cesarean section, gestational age <37+0 weeks, rupture of the membranes at the time of the labor ward visit and women admitted because of non-reactive fetal heart rate in the latent phase. Furthermore, women with an interval >10 days between use of therapeutic rest and delivery were excluded. Women were included regardless of whether they were discharged or admitted to the labor ward.

We divided the women into two groups: women who were treated with therapeutic rest and women who were not. Any medication used for therapeutic rest was registered in the electronic patient record and handed out by the midwife either for administration at the labor ward or for self-administration by the pregnant woman. Women who at a later occasion reported to the midwife that they did not take the medication, were relocated to the group of women who were not treated with therapeutic rest.

All data variables were extracted from the women's and the neonates' electronic medical records and registered in predefined electronic data extraction forms.

2.2 | Baseline characteristics

Maternal characteristics included age, pre-pregnancy body mass index (BMI), gestational age at birth, smoking (yes/no), cohabiting/married (yes/no) and level of prenatal care. We categorized the women into three levels of prenatal care: standard, extended (women of young age, with overweight defined as BMI >30, difficulties due to immigration, socioeconomic or psychosocially vulnerable life circumstances) and high level of prenatal care (women with substance abuse, medication influencing the fetus or severe comorbidity).

2.3 | Outcomes

Our primary outcomes were admission to the neonatal intensive care unit (NICU) within 24 hours after delivery (yes/no) and neonatal delivery room resuscitation (yes/no). We defined neonatal resuscitation as any of the following treatments: ventilation, external heart massage, intubation or pharmacological resuscitation. Secondary perinatal outcomes included use of cardiotocography (CTG) during labor (yes/no), non-reactive fetal heart rate (yes/no) as classified by The International Federation of Gynecology and Obstetrics consensus guidelines on intrapartum fetal monitoring 1985[22] including abnormal and pathological CTG pattern, meconium-stained amniotic fluid (yes/no), pediatric assistance requested in the delivery room (yes/no), umbilical cord arterial pH value ≤7.1 (yes/no), umbilical cord arterial standard base excess < −10 mmol/L (yes/no) and 5-min Apgar score <7 (yes/no).

Further, we collected data on the following labor outcomes: duration of labor defined as the period from the self-reported beginning of contractions until delivery, admission to the hospital during therapeutic rest/in the latent phase (yes/no), duration from time of seeking care at the labor ward in the latent phase to delivery, duration from therapeutic rest to delivery, cervical length and dilatation and frequency of contractions at the first labor ward visit, amniotomy at any point in labor (yes/no), oxytocin augmentation during labor (yes/no), epidural analgesia (yes/no), pudendal nerve block (yes/no) and mode of delivery (vaginal, assisted vaginal (ventouse or forceps), cesarean section).

Information about medication included types and combinations of drugs, doses, repeated doses and administration routes.

Based on the Danish Quality Database for Newborns Annual Report 2020 on neonatal admission after delivery at term, the neonatal admission rate of full-term newborns is 2%.[23] An American study reported neonatal admission of 10% for newborns delivered after therapeutic rest.[14,24] We anticipated a more conservative 7% neonatal admission rate after therapeutic rest. Based on this assumption, inclusion of 800 women with an equal distribution between the two groups would result in a power of 82% to detect a difference in neonatal admission between the groups.

2.4 | Statistical analyses

Our data analyses were performed using STATA/MP 17.0. Descriptive statistics in the two groups are presented as counts and percentages for categorical variables, mean and standard deviation (SD) for continuous Gaussian variables and median and interquartile range (IQR) for continuous, non-Gaussian variables.

Logistic regression was used to estimate crude and adjusted odds ratios (aOR) with 95% confidence intervals (CI) for perinatal and labor outcomes. Based on a Directed acyclic graph (Appendix S1) we fitted two models. In the first model, we adjusted for the following confounders: maternal age (continuous), pre-pregnancy BMI (BMI > or <30 kg/m^2), length of gestation at birth (continuous), smoking status (yes/no), cohabiting/married status (yes/no), prenatal care (standard/extended care) and the number of therapeutic rest administrations (categorical data). In the second model, we further adjusted for cervical dilatation (0–2 cm; ≥3 cm) and the number of contractions per 10 min (0–2; ≥3) at the first labor ward visit, as this may further affect the labor outcomes independently of the use of therapeutic rest.

We evaluated the primary neonatal outcomes and pediatric assistance at the delivery room in a sensitivity analysis in women who delivered <20 hours from time of seeking care and in women who delivered less than 20 hours from treatment with therapeutic rest *or* seeking care.

Further, we performed a sensitivity analysis and evaluated the primary neonatal outcomes and pediatric assistance at the delivery room, with women delivering after >20 hours from therapeutic rest grouped together with the unexposed women who were not treated with therapeutic rest, as most medication will be eliminated by that time.

2.5 | Ethics statement

Permission for the study was granted by Aarhus University Hospital on August 30, 2021 and Central Region Denmark on February 2, 2022 (1–45–70-85-21).

3 | RESULTS

A total of 3716 women presented at the labor ward throughout the study period, of which 2916 were excluded according to the exclusion criteria. We included 800 nulliparous singleton pregnant women: 414 of these women (51.8%) were treated with therapeutic rest and 386 (48.2%) were not (Figure 1).

Maternal characteristics are presented in Table 1. Women who were treated with therapeutic rest had a slightly longer length of gestation at birth, were less often cohabitating and received higher levels of prenatal care. There were no differences between the two groups regarding age, pre-pregnancy BMI or smoking status.

Further, women who were treated with therapeutic rest presented with a less favorable cervical ripening and fewer contractions per 10 minutes during the first labor ward visit than women who were not treated with therapeutic rest (Table 1).

Data regarding types, doses, combinations and number of repeated treatments for the medication used for therapeutic rest are presented in Table 2.

Of the women who were treated with therapeutic rest, a total of 311/414 (75.1%) had therapeutic rest once, 83/414 (20.0%) had therapeutic rest twice, 19/414 (4.6%) had therapeutic rest three times and 1/414 (0.2%) had therapeutic rest four times.

The most frequently used medication for therapeutic rest was a combination of 1000 mg paracetamol, 0.125 mg triazolam and 25 or 50 mg codeine, which was given to 206/414 (49.8%) of women treated for the first time. The combination of 1000 mg paracetamol, 10 mg zolpidem, and 25 or 50 mg codeine was the second most used first-time treatment (29.2%), next to 10 mg morphine as a single intramuscular injection (10.4%).

An intramuscular injection of 10 mg morphine was the most frequently used treatment in the group of women who were treated with therapeutic rest two (10.9%) and three times (2.9%), respectively.

Table 3 shows perinatal and labor outcomes. There was no significant difference in the risk of neonatal admission after delivery between women who were treated with (9.2%) or without (6.5%) therapeutic rest (aOR 1.2, 95% CI 0.4–3.1). Additionally, there was no significant difference in neonatal resuscitation between women treated with (2.4%) or without (3.1%) therapeutic rest (aOR 0.7, 95% CI 0.1–4.0).

There were no differences in the use of CTG during labor, non-reactive fetal heart rate, pediatric assistance requested at or immediately after birth, umbilical cord arterial pH-value ≤7.1 and standard base excess <10 mmol/L and 5-min Apgar score <7 between the groups (Table 3).

Therapeutic rest was associated with a lower risk of meconium-stained amniotic fluid in the adjusted model (aOR 0.5, 95% CI 0.3–0.9). The risk of several obstetrics interventions was higher in the treated group; however, this association disappeared in the adjusted models.

The duration of labor was significantly longer in the group of women who were treated with therapeutic rest than in the group of women who were not (median [IQR], hours; 45.5 [31–60.5] vs 25.3 [18–34.5]). Furthermore, women who were treated with therapeutic rest had a significantly longer duration from the time of seeking care at the labor ward in the latent phase to delivery (median [IQR], hours; 22 [14.5–31] vs 12.5 [8–19]). Median time interval from administration of medication to delivery among women treated with therapeutic rest was 20 hours (IQR 13–28).

In our sensitivity analysis, we found no differences in neonatal admission, neonatal resuscitation or pediatric assistance at the delivery room between women with delivery <20 and >20 hours after seeking care or treatment with therapeutic rest. However, the numbers were small (Appendix S2). Further, there were no differences in neonatal admission, neonatal resuscitation or pediatric assistance at the delivery room when women with delivery <20 hours after treatment with therapeutic rest were compared

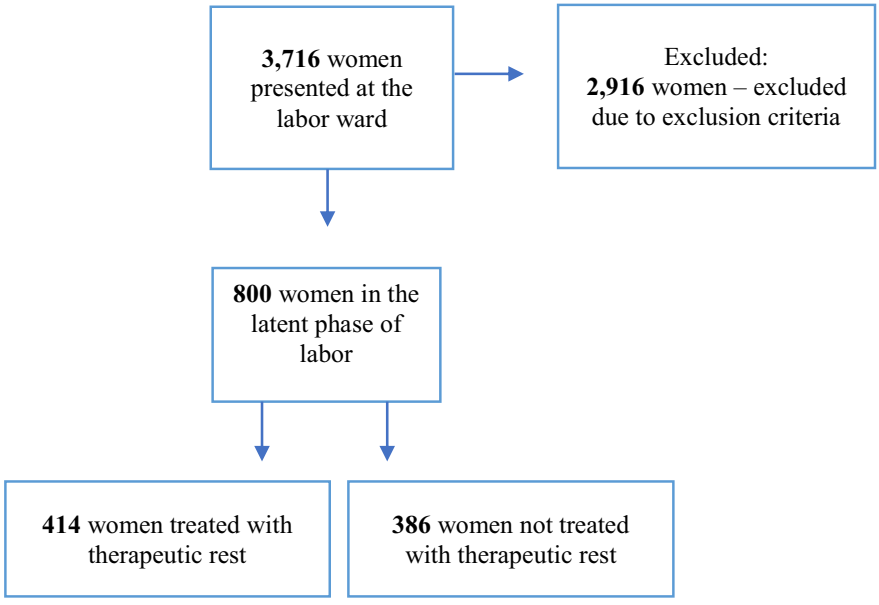

FIGURE 1 Flow diagram of the inclusion of women in the study.

TABLE 1 Maternal characteristics of women presenting at the labor ward in the latent phase of labor treated with or without therapeutic rest.*

Variable	Therapeutic rest	
	Yes ($n=414$)	No ($n=386$)
Maternal age, mean (± SD) years	28.2 ± 4.2	28.3 ± 4.1
Pre-pregnancy BMI, median (IQR) kg/m^2	22.8 (20.7–25.7)	22.4 (20.8–24.9)
Length of gestation at birth, weeks+days, median (IQR) weeks + days	40+5 (40+0 to 41+2)	40+3 (39+5 to 40+6)
Smoking, *n* (%)	13 (3.15)	10 (2.6)
Cohabiting/married, *n* (%)	382 (92.7)	370 (96.9)
Level of prenatal care, *n* (%)		
Standard care, *n* (%)	287 (69.7)	284 (74.5)
Extensive care, *n* (%)	116 (28.2)	93 (24.4)
Highest level of care during pregnancy, *n* (%)	9 (2.2)	4 (1.0)
Cervical length, *n* (%)[a]		
3 cm	2 (0.5)	0 (0)
2 cm	13 (3.3)	10 (2.8)
1 cm	52 (13.3)	48 (13.4)
0 cm	325 (82.9)	301 (83.8)
Cervical dilatation, *n* (%)[a]		
0 cm	14 (3.5)	4 (1.0)
1–2 cm	300 (74.1)	218 (56.9)
3–4 cm	89 (21.9)	153 (40.0)
>4 cm	2 (0.5)	8 (2.1)
Number of contraction per 10 minutes, (*n*%)[a]		
0	0 (0)	1 (0.3)
1–2	302 (74.7)	218 (60.2)
3–4	99 (24.5)	138 (38.1)
>5	3 (0.7)	5 (1.4)
Admission during therapeutic rest or in the latent phase of labor, *n* (%)	140 (33.8)	151 (39.1)

*Therapeutic rest is defined as use of morphine, other opioid or opioid analogs, and/or sedative medication, alone or in combination with simple analgesics.

[a]At the first labor ward visit in the latent phase of labor.

Missing frequencies: BMI, smoking, cohabitation, level of prenatal care (therapeutic rest group), cervical dilatation (no therapeutic rest group) – <1%; level of prenatal care (no therapeutic rest group), cervical dilatation (therapeutic rest group), number of contractions (therapeutic rest group) – 1–2.5%; cervical length, number of contractions (no therapeutic rest group) – 2.5–7%.

with women with delivery >20 hours after treatment with therapeutic rest and women who were not treated with therapeutic rest (Appendix S2).

4 | DISCUSSION

In a cohort of 800 nulliparous women who sought hospital care in the latent phase of labor, we found no increased risk for neonatal admission or resuscitation, other adverse perinatal outcomes, adverse labor outcomes or obstetric interventions in women and their neonates following treatment with therapeutic rest as compared with those who were not.

Given the potential adverse effects of opioids and hypnotics/sedatives alone, it is concerning that the combined effect of these medications has not been elucidated previously. Three prior studies addressed the impact of therapeutic rest regimens on perinatal outcomes; all of them included fewer than 100 participants of mixed parity, and the medication regimens were different to ours.

An American study evaluated the effect of more than 10 mg morphine for therapeutic rest in 58 women. None of the infants from this study was admitted to the NICU and there were no

TABLE 2 Type, dose, combinations and administration route of medication used during the latent phase in the group of women who were treated with therapeutic rest.

1st therapeutic rest treatment	*n* (%)	2nd therapeutic rest treatment	*n* (%)	3rd therapeutic rest treatment	*n* (%)
Medication during the first therapeutic rest	**414 (100)**	**Medication during the second therapeutic rest**	**103 (24.9)**	**Medication during the third therapeutic rest**	**20 (4.8)**
Paracetamol 1000 mg + triazolam 0.125 mg + codeine 25 or 50 mg	206 (49.8)	Morphine 10 mg i.m.	45 (10.9)	Morphine 10 mg i.m.	12 (2.9)
Paracetamol 1000 mg + Zolpidem 10 mg + codeine 25 or 50 mg	121 (29.2)	Paracetamol 1000 mg + triazolam 0.125 mg + codeine 25 or 50 mg	30 (7.2)	Paracetamol 1000 mg + triazolam 0.125 mg + codeine 25 mg	3 (0.7)
Morphine 10 mg i.m.	43 (10.4)	Paracetamol 1000 mg + zolpidem 10 mg + codeine 25 or 50 mg	9 (2.2)	Paracetamol 1000 mg + zolpidem 10 mg + codeine 25 mg	2 (0.5)
Paracetamol 1000 mg + codeine 25 or 50 mg	34 (8.2)	Paracetamol 1000 mg + codeine 25 or 50 mg	9 (2.2)	Paracetamol 1000 mg + codeine 50 mg	1 (0.2)
Triazolam 0.125 mg + Codeine 25 or 50 mg	3 (0.7)	Morphine 5 mg i.m.	3 (0.7)	Morphine 5 mg i.m. + morphine 5 mg i.v.	1 (0.2)
Morphine 5 mg i.m.	2 (0.5)	Morphine 6 mg i.m.	2 (0.5)	Codeine 50 mg	1 (0.2)
Paracetamol 1000 mg + zolpidem 10 mg	2 (0.5)	Morphine 8 mg i.m.	1 (0.2)	–	–
Zolpidem 10 mg + codeine 25 or 50 mg	1 (0.2)	Morphine 7.5 mg i.m.	1 (0.2)	–	–
Morphine 5 mg i.m. + triazolam 0.125 mg	1 (0.2)	Morphine 5 mg i.m. + morphine 5 mg i.v.	1 (0.2)	–	–
Codeine 25 mg	1 (0.2)	Paracetamol 1000 mg + zolpidem 10 mg	1 (0.2)	–	–
–	–	Triazolam 0.125 mg	1 (0.2)	–	–

Route of administration is oral administration except when intramuscular (i.m.) or intravenous injection (i.v.) is registered.
One woman was treated with therapeutic rest (10 mg of morphine i.m.) four times during the latent phase.

adverse maternal outcomes.[10] In a randomized study, the analgesic efficacy of intramuscular pethidine was compared with placebo in 50 women; no differences in adverse labor and perinatal outcomes were seen.[21] Most recent, therapeutic rest with intramuscular morphine and promethazine was compared with no therapeutic rest in women who either accepted or declined therapeutic rest in a prospective cohort study.[14] There were no differences in low Apgar score, low umbilical cord pH values or adverse obstetrical outcomes, but a slightly higher frequency of unplanned neonatal admission with therapeutic rest (10%) than without (0%).[14,24] Overall, our study supports and strengthens the evidence from previous studies that therapeutic rest does not increase the risk of adverse perinatal outcomes. Our data did suggest that therapeutic rest was associated with a lower risk of meconium-stained amniotic fluid.

The possible adverse effect of therapeutic rest on perinatal outcomes is likely to depend to a large extent on the duration from exposure of the medication to delivery. Half-lives of opioids such as codeine and morphine are typically 2–4 hours in adults but have significantly longer half-life in neonates,[25,26] whereas the half-life of anxiolytics/hypnotics can be 1.4–5.5 hours in adults, depending on the type of drug.[18–20]

Only one prior study on therapeutic rest reported on the duration from the administration of medication to delivery, which was about 5–6 hours.[21] Our results showed a median duration from the administration of medication to delivery of 20 (13–28) hours, an interval which suggests that the medication would probably have been eliminated by the time of delivery. This time factor is likely to have limited the ability to evaluate the immediate association between therapeutic rest and adverse perinatal outcomes. It was reassuring that even in the subgroup analysis of women in our study with a shorter duration from administration of the medication to delivery, there was no association with adverse neonatal outcomes (Appendix S2).

Women who were treated with therapeutic rest had a poorer cervical ripening and fewer contractions in the latent phase of labor

TABLE 3 Perinatal and labor outcomes after use of therapeutic rest* in the latent phase of labor vs no therapeutic rest.

Variable	Therapeutic rest		OR (95% CI)	aOR (95%CI)[a]	aOR (95%CI)[b]
	Yes ($n=414$)	No ($n=386$)			
Perinatal outcomes					
Admission to NICU, *n* (%)	38 (9.2)	25 (6.5)	1.5 (0.8–2.6)	1.3 (0.5–3.4)	1.2 (0.4–3.1)
Neonatal resuscitation, *n* (%)	10 (2.4)	12 (3.1)	0.8 (0.3–2.0)	0.7 (0.1–4.0)	0.7 (0.1–4.0)
Use of CTG during labor, *n* (%)	363 (87.7)	295 (76.4)	2.2 (1.5–3.3)	0.8 (0.3–2.0)	0.8 (0.3–2.2)
Nonreactive fetal heart rate, *n* (%)	285/363 (78.5)	240/295 (81.4)	0.8 (0.6–1.3)	1.1 (0.5–2.2)	1.3 (0.6–2.8)
Meconium-stained amniotic fluid, *n* (%)	135 (32.6)	120 (31.1)	1.1 (0.8–1.5)	0.6 (0.3–1.0)	0.5 (0.3–0.9)
Pediatric delivery room assistance, *n* (%)	105 (25.4)	76 (19.7)	1.4 (1.0–2.0)[c]	1.0 (0.5–1.9)	1.0 (0.5–2.0)
Umbilical cord arterial pH value ≤7.1, *n* (%)	24 (7.2)	18 (5.8)	1.2 (0.6–2.5)	2.3 (0.6–8.4)[d]	2.3 (0.6–8.7)[d]
Umbilical cord arterial SBE < −10 mmol/L, *n* (%)	18 (5.4)	11 (3.6)	1.5 (0.7–3.3)	1.8 (0.4–7.2)[e]	1.9 (0.4–7.9)[e]
5-min Apgar score <7, *n* (%)[f]	3 (0.7)	5 (1.3)	0.6 (0.1–2.9)	–	–
Labor outcomes					
Amniotomy, *n* (%)[g]	197 (47.6)	147 (38.1)	1.5 (1.1–2.0)	0.7 (0.4–1.2)	0.7 (0.4–1.3)
Oxytocin augmentation, *n* (%)	200 (48.3)	118 (30.6)	2.1 (1.6–2.9)	0.9 (0.5–1.6)	0.8 (0.4–1.5)
Epidural analgesia, *n* (%)	230 (55.6)	149 (38.6)	2.0 (1.5–2.7)	1.0 (0.6–1.7)	0.9 (0.5–1.6)
Pudendal nerve block, *n* (%)	35 (8.5)	36 (9.3)	0.9 (0.5–1.5)	1.0 (0.4–2.5)	1.2 (0.4–3.1)
Vaginal delivery, *n* (%)	293 (70.8)	313 (81.1)	0.6 (0.4–0.8)	0.8 (0.4–1.4)	0.7 (0.4–1.4)
Vacuum-assisted delivery, *n* (%)	58 (14.0)	45 (11.7)	1.2 (0.8–1.9)	1.2 (0.6–2.6)	1.4 (0.6–3.2)
Cesarean section, *n* (%)	63 (15.2)	29 (7.5)	2.2 (1.4–3.7)	1.4 (0.6–3.1)	1.2 (0.5–2.9)

*Therapeutic rest is defined as use of morphine, other opioid or opioid analogs, and/or sedative medication, alone or in combination with simple analgesics.

[a]aOR: adjusted for maternal age, BMI, length of gestation at birth, smoking, cohabiting level, prenatal care and the number of therapeutic rest administrations.

[b]aOR: further adjusted for cervical dilatation and number of uterine contractions.

[c]Not significant.

[d]Following variables were omitted from the model because of collinearity: BMI > or <30, smoking status, cohabiting status.

[e]The following variables were omitted from the model because of collinearity: smoking status, cohabiting status.

[f]It was not possible to perform logistic regression analysis because there were too few observations within each category.

[g]Reasons for amniotomy include augmentation of labor, need for internal CTG monitoring, suspected placental abruption or determination of the color of amniotic fluid.

Number of missing data in the following categories, therapeutic rest vs non-therapeutic rest groups, respectively: umbilical cord arterial pH: 80/414 vs 79/386, umbilical cord arterial SBE: 81/414 vs 80/386, 5-min Apgar score <7: 3/414 vs 0/386.

compared with the group of women who were not. These factors are likely to have contributed to the clinical decision to offer therapeutic rest and may also act as predictors of a more complicated delivery course, as longer latent phases may increase the chance that women seek care in the latent phase. It is reassuring that even without confounder adjustment, most of the adverse outcomes in our sample did not differ between the two groups.

A number of non-pharmacological obstetric practices to assist women in the latent phase are available, such as reassurance and information about the latent phase from the healthcare provider, massage or immersion in water, but evidence on these options is limited or uncertain.[27]

The findings of this study may not be applicable to countries or settings with different management options of women in the latent phase including using other types and combinations of medications for therapeutic rest.

Our study is limited by its retrospective design. We constructed a directed acyclic graph (Appendix S1) to address potential confounding bias but, nevertheless, residual and unknown confounding may persist. In particular, the more subjective provider-based reasons to offer therapeutic rest to one woman and not to another are difficult to capture and to adjust for. In our study we could not evaluate the effect of therapeutic rest on the mother–child interaction, breastfeeding or the women's experience of the labor. Also, possible

long-term effects of the medication on the neonate are uncertain. Finally, as in other studies using prescription data, there is a risk of misclassification if some women did not take all or some components of the therapeutic rest medication given and did not give this information to the providers.

With regard to paracetamol, as it is available over the counter, we cannot account for the number of women who used paracetamol. As the women in the non-exposure group went home without any medications prescribed from the hospital, which was most likely a consensus decision between the woman and the caregiver, we assume that few women went home to self-medicate with paracetamol. Women treated with medications with possible respiratory depression effects in the newborns such as morphine, codeine or benzodiazepines would all be in our exposure group.

We performed our power estimates under the assumption of NICU admissions of 7% after use of therapeutic rest, which is conservative compared with the existing literature. However, there is still an 18% risk of missing an existing risk difference, which can be addressed in larger studies.

The major strength of our study is its size, with more than 400 women given therapeutic rest, the largest sample published to this date,[10,14,21] thus allowing for detection of rare events such as NICU admission and resuscitation. Furthermore, with restriction of the sample to nulliparous women only, we enhanced the homogeneity of the study population.[28,29] Data were extracted directly from medical records for the purpose of this study into a structured data capture form.

5 | CONCLUSION

We found that poly-pharmacological therapeutic rest is a safe regimen in nulliparous women for managing the latent phase of labor in an outpatient setting. Our finding adds important information for the reassuring counseling of the pregnant women who are uncertain about adverse effects of therapeutic rest, as our results did not give rise to concerns about safety aspects of the treatment. To our knowledge, there are no available international guidelines regarding the use of therapeutic rest and our data add information to a drought of evidence despite the well-known clinical situation in every labor ward worldwide.

AUTHOR CONTRIBUTIONS

The study was initiated by NTB, JG and SB. All authors contributed to the design of the study. Acquisition of data was performed by NTB. Statistical analysis was performed by NTB and IM. NTB drafted the paper. JG, IM and SB reviewed and edited the paper repeated times during the process. All authors approved the last version of the article.

CONFLICT OF INTEREST STATEMENT

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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